Detection of Newborns at Risk for Pathologic Hyperbilirubinemia: A Handheld End-Tidal CO Measurement Device For Quantification Of Hemolysis

George F. Tidmarsh, MD, PhD
Associate Professor, Pediatrics and Neonatology
Stanford University School of Medicine

Summary

- **End-tidal CO is the most direct and accurate measurement of hemolysis**
- **Hand-held device for measurement of end tidal carbon monoxide (ETCO) indicates hemolysis**
- **Potential application diagnosing newborns at-risk for adverse outcomes of hyperbilirubinemia (jaundice)**
  - **Potential to improve healthcare efficiency and patient outcomes by focusing care to those in need allowing others early discharge**
- **Offers significant advantages vs. current laboratory test procedures**
  - **More accurate and faster diagnosis**
  - **Less expensive**
  - **Non-invasive**
  - **Portable hand-held**
  - **Simple and easy to use for physicians and nurses**

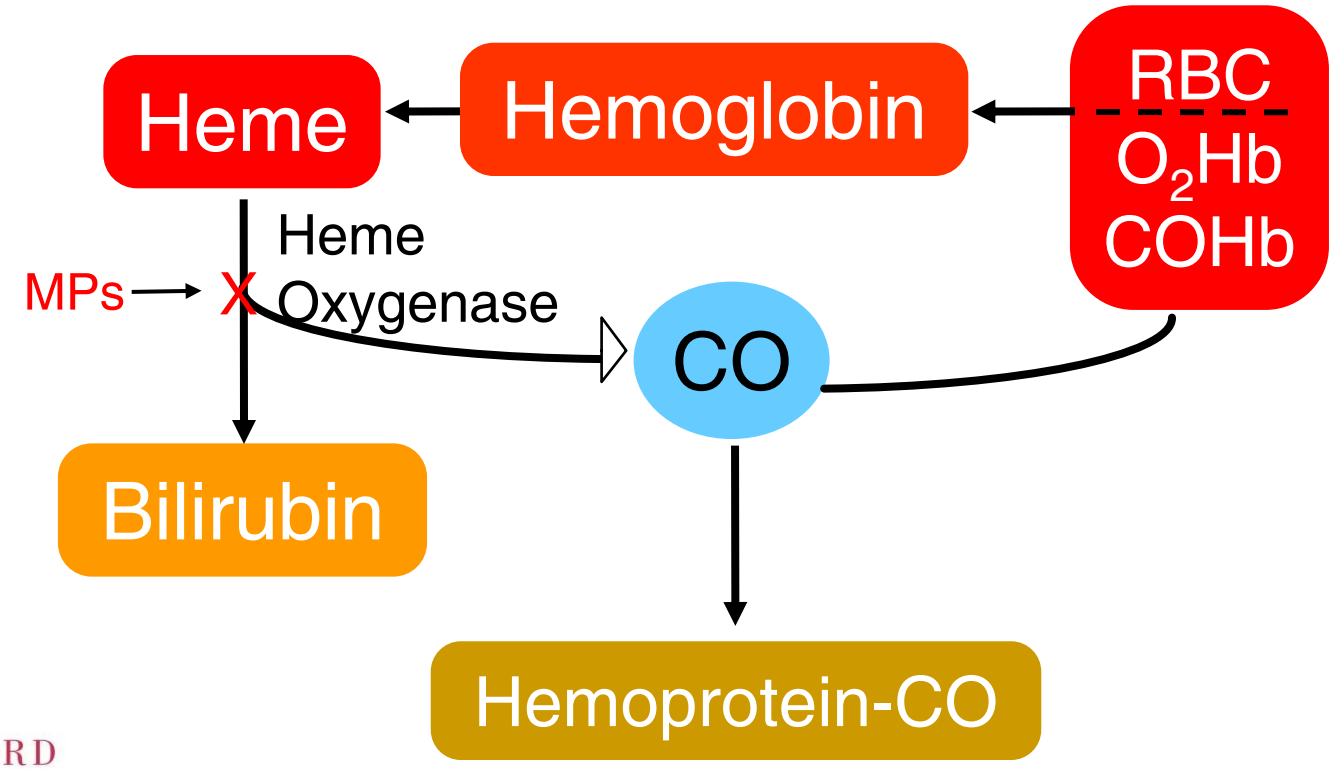
The Science: Hemolysis and End Tidal Carbon Monoxide (ETCO)

What is Hemolysis?

- **Breakage of red blood cells (RBC's) releasing hemoglobin**
- **When RBC breakdown exceeds the body's ability to compensate, anemia develops:**
  - **Fatigue**
  - **Potential heart failure**
- **When hemoglobin release exceeds the liver's ability to compensate, hyperbilirubinemia (jaundice) develops**
- **Examples of hemolytic diseases:**
  - **Isoimmune Disorders: ABO, Rh incompatibilities (Fetal hydrops)**
  - **Autoimmune Hemolytic Anemia (systemic lupus erythematosus, mononucleosis)**
  - **Hemoglobinopathies: Sickle Cell, Thalasemia**
  - **Hemoglobinuria: PNH**
  - **Enzyme Deficiencies: G-6-PD Deficiency**
  - **Red Cell Membrane Defects: Hereditary Spherocytosis, Hereditary Elliptocytosis.**

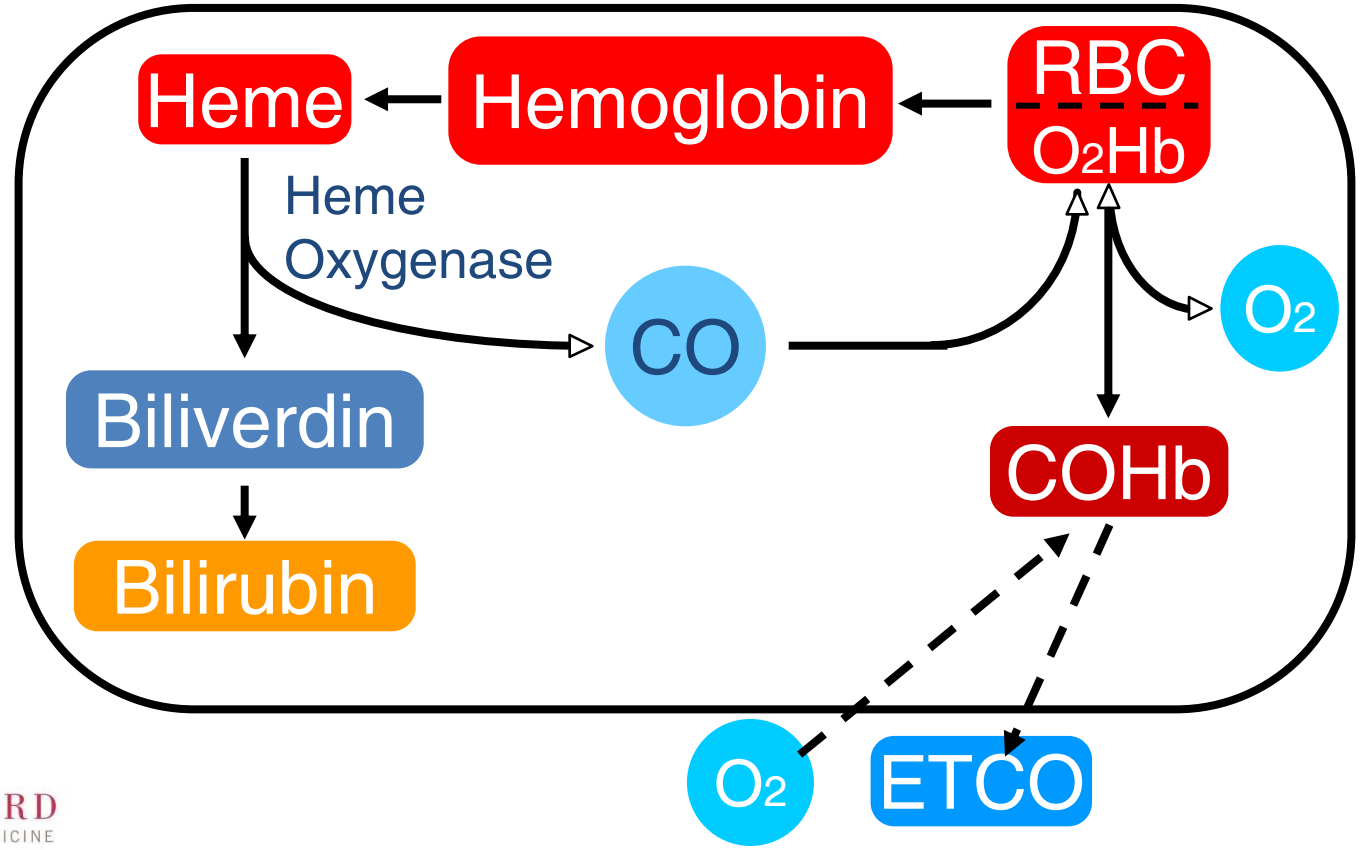
Hemolysis and Carbon Monoxide

- **CO produced in a 1:1 molar ratio with bilirubin and may bind locally to hemoproteins in tissue cells**
- **CO ultimately equilibrates with oxyhemoglobin in RBC's to form carboxyhemoglobin (measured by chromatography)**
- **Metalloporphyrins inhibit heme oxygenase**



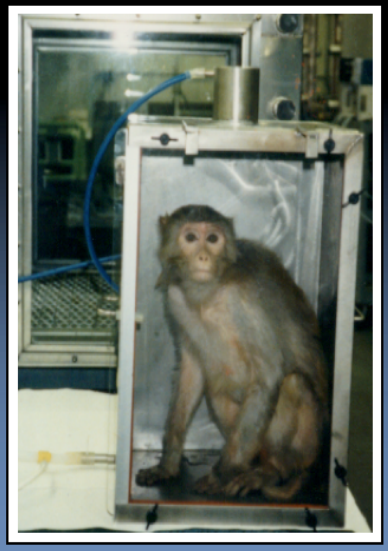
Carbon Monoxide Pathway

- **When carboxyhemoglobin reaches the lung, oxygen displaces the CO which is then excreted in the breath**
- **Rate of CO excretion is an index of endogenous heme degradation as well as bilirubin formation**

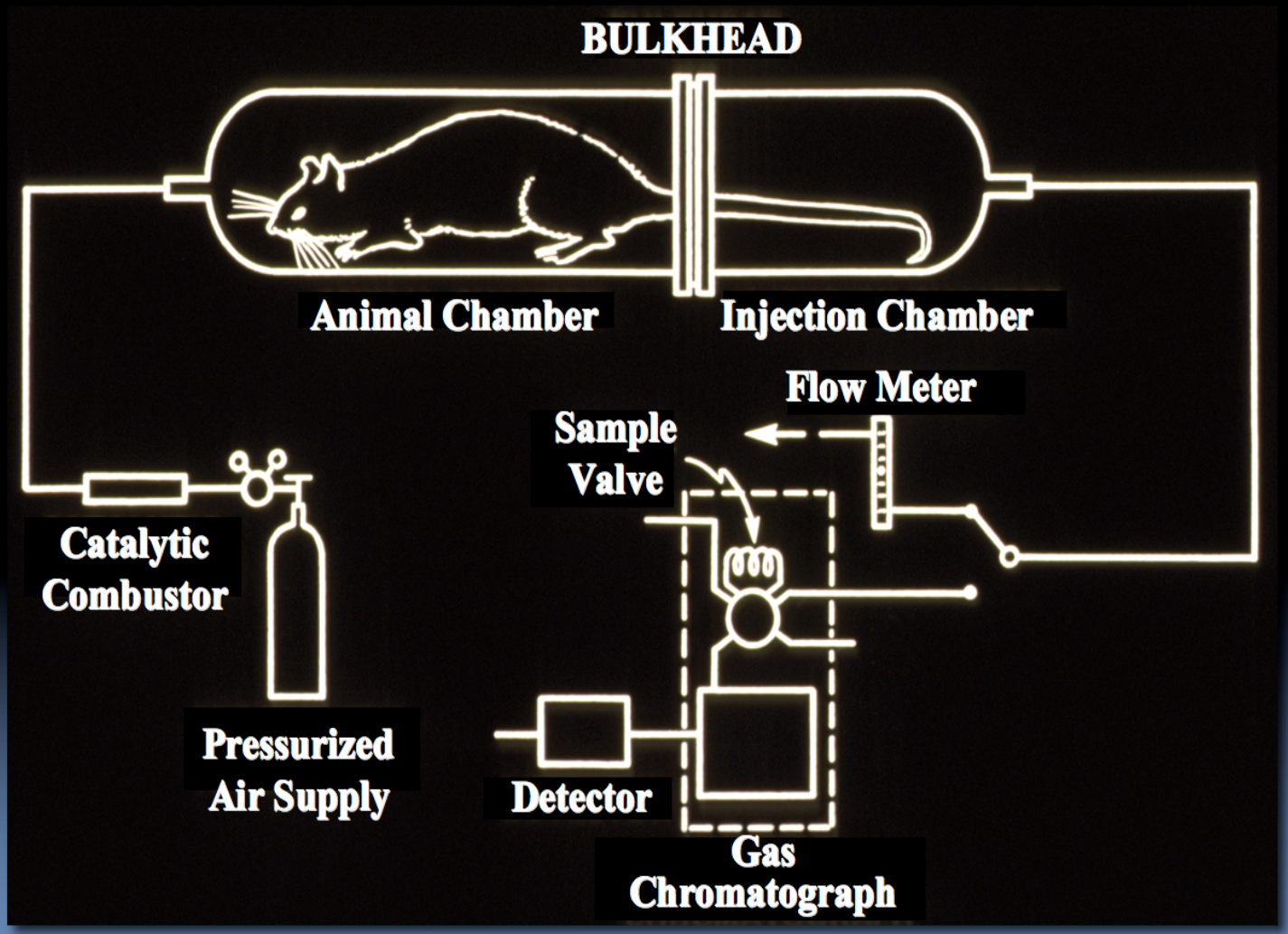


VECO MEASUREMENTS IN DIFFERENT SPECIES

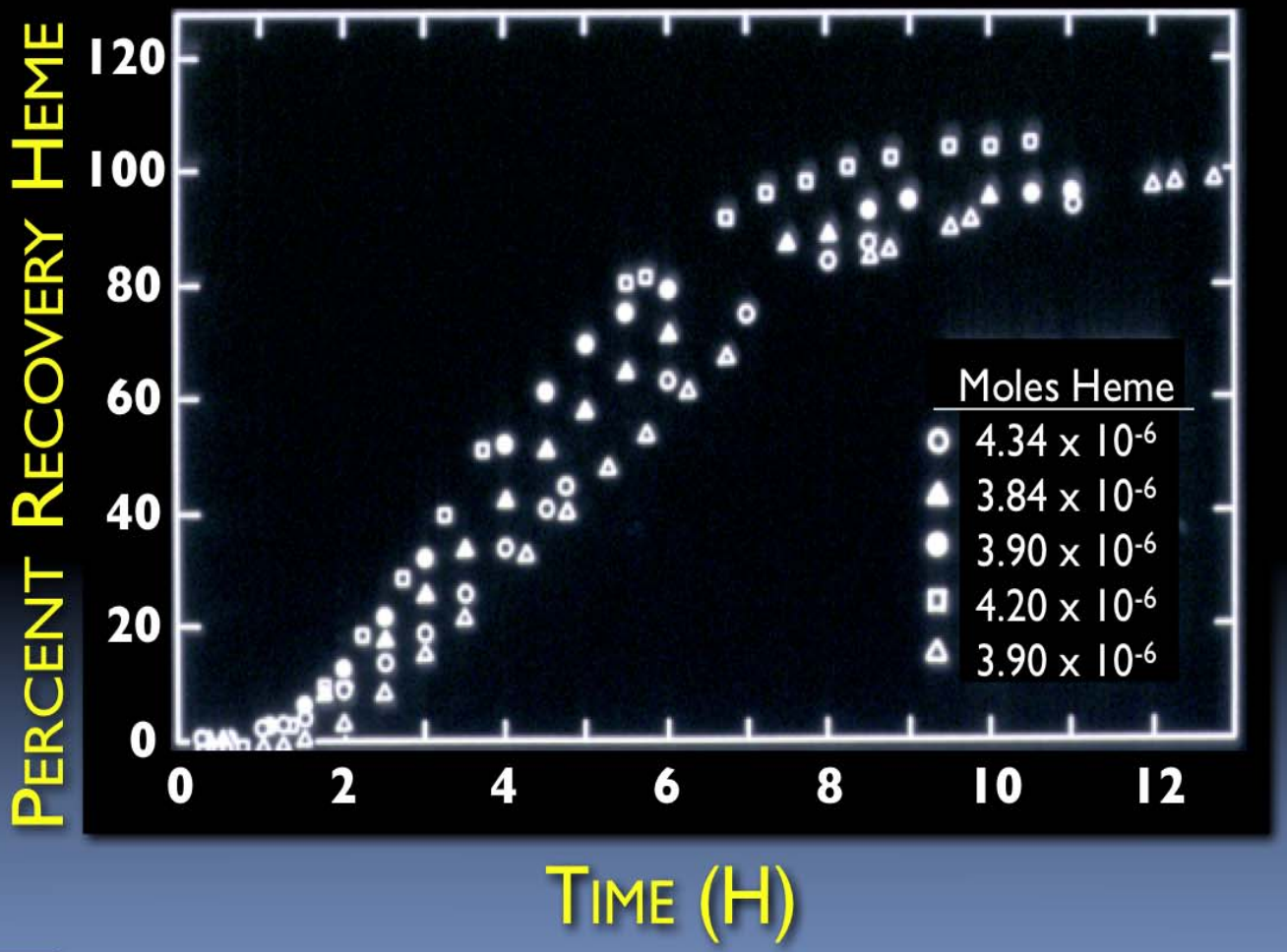
Monkeys



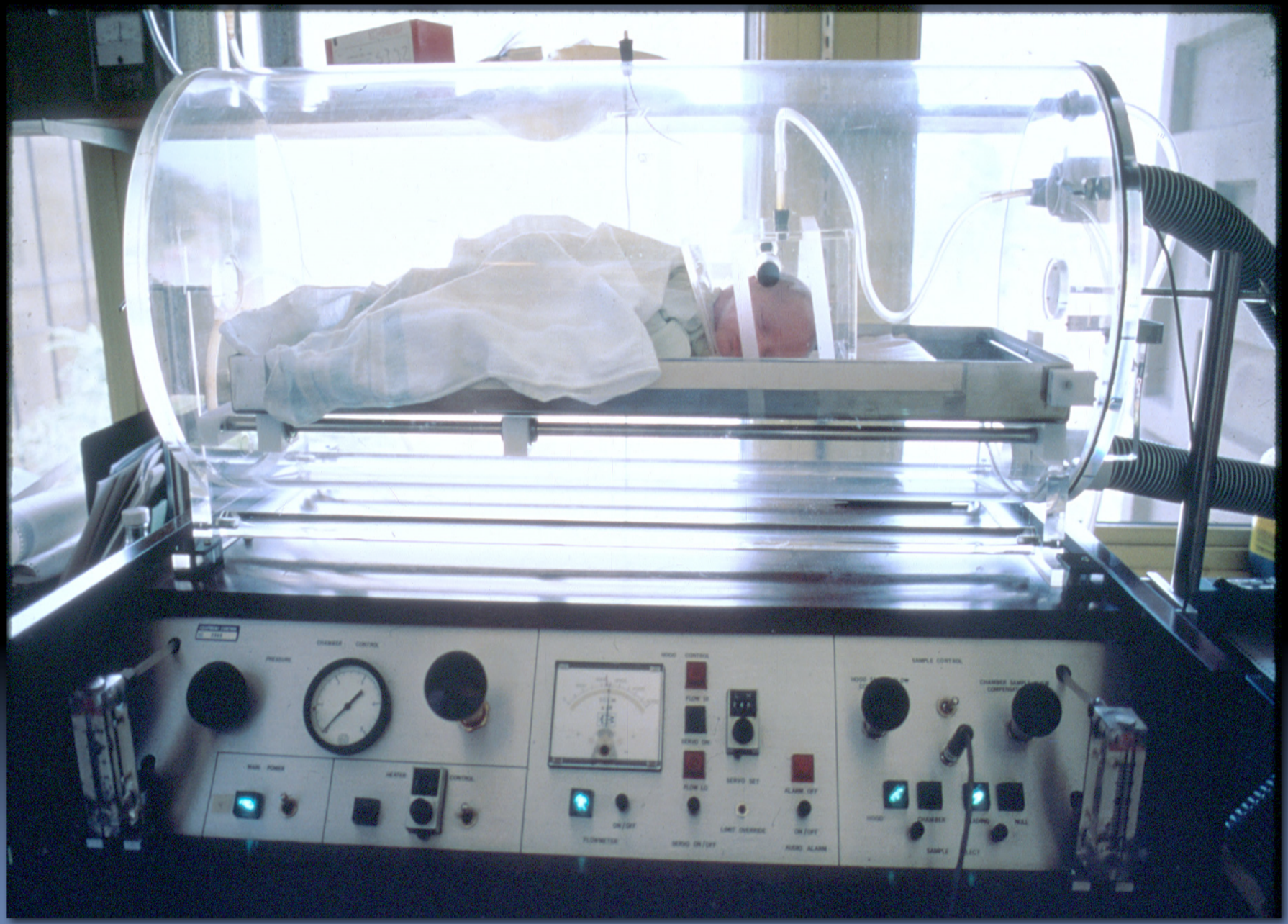
A Schematic Diagram of Gas Collection Apparatus



Percent Recovery of Injected Heme Over Time

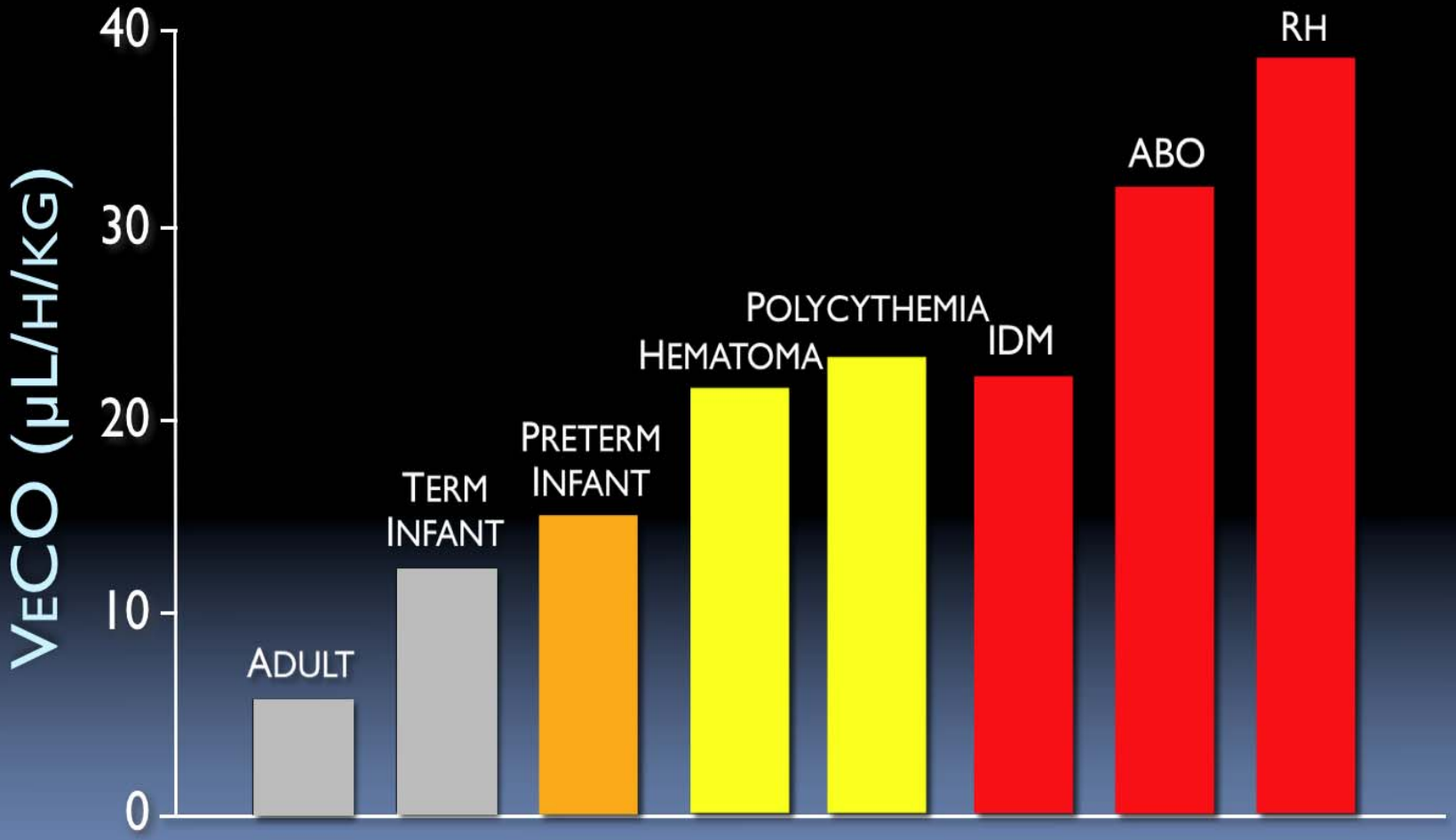


STANFORD
SCHOOL OF MEDICINE



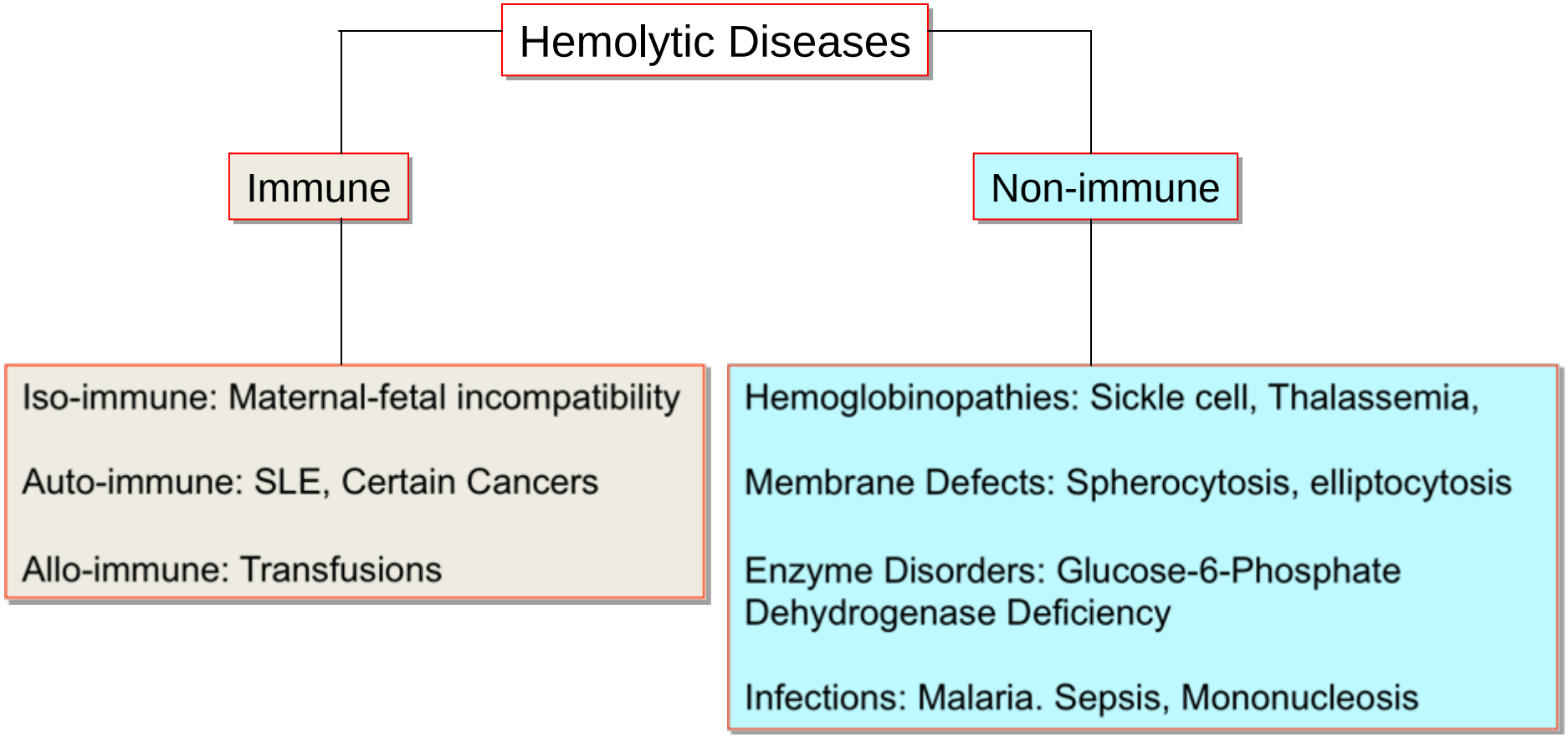
STANFORD
SCHOOL OF MEDICINE

VECO LEVELS UNDER DIFFERENT CONDITIONS



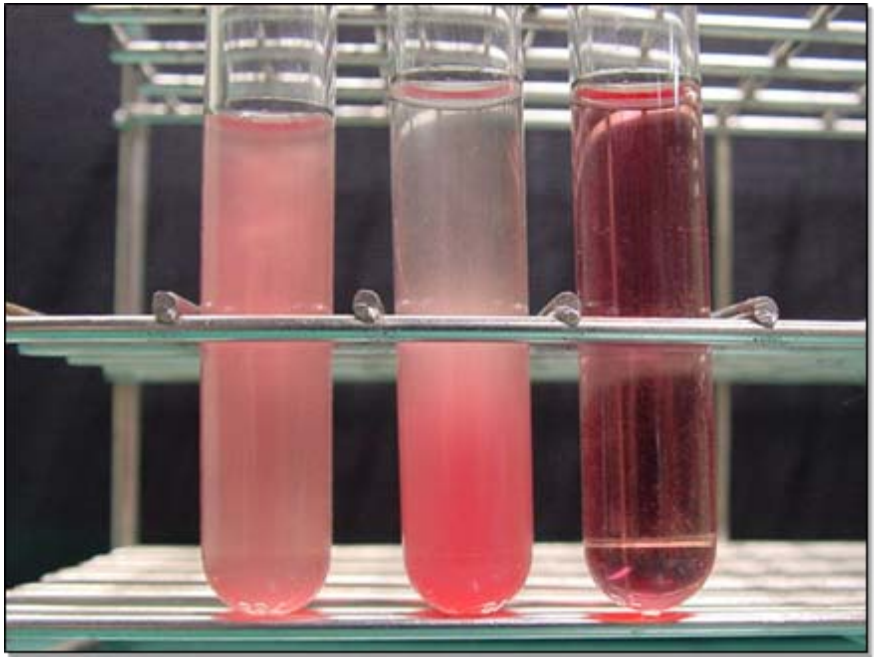
STANFORD SCHOOL OF MEDICINE

Types of Hemolytic Disease



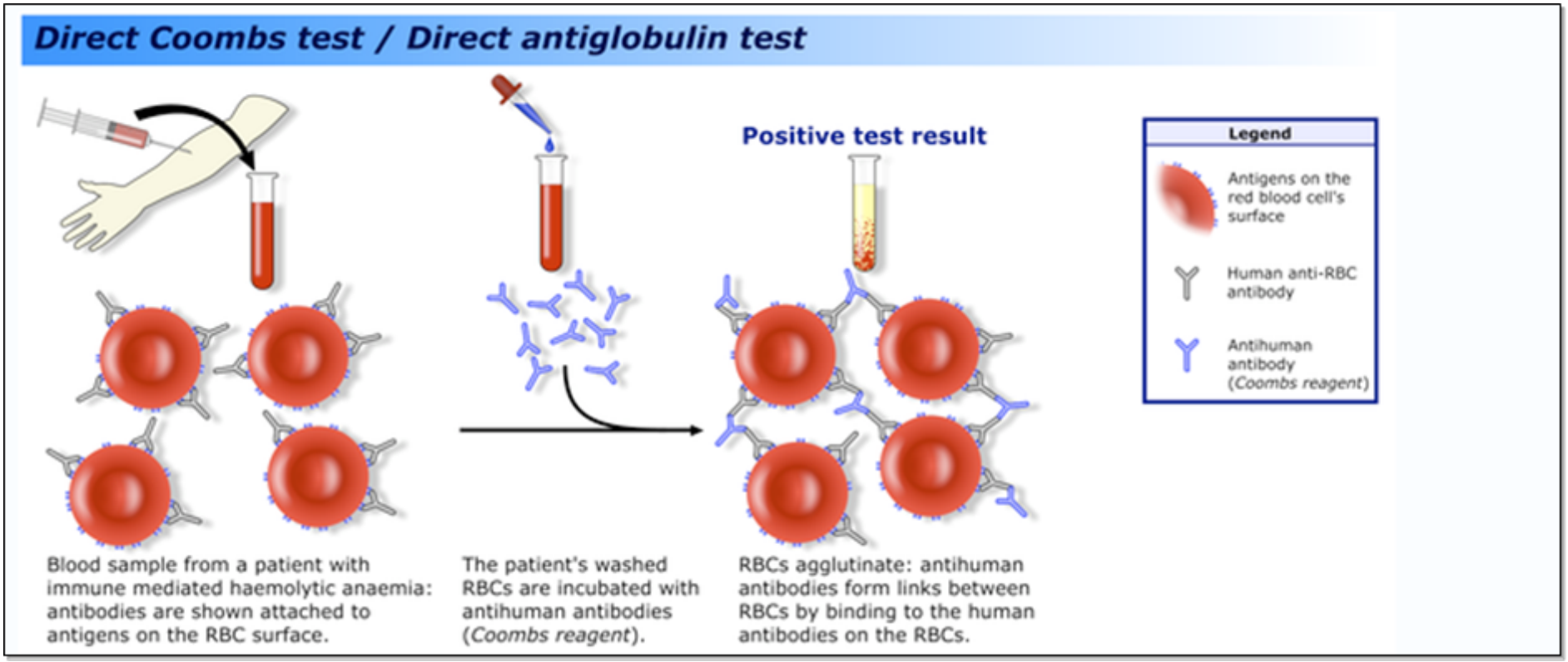
Hemolysis: *Standard Diagnostic Approach*

- **Typical combination of laboratory blood tests:**
  - **Coombs Antiglobulin Test**
    - **Direct**
    - **Indirect**
  - **Type and Cross**
  - **Reticulocyte Count**
  - **At least one CBC**



Coomb's Test - Direct Antiglobulin Test (DAT)

- **Detects antibodies bound to surface of red blood cells**
- **Positive test indicates an immune mechanism is attacking the patients own RBC's**



Coombs Test - Limitations

- **Detects antibiodies only; a positive DAT is not always associated with evidence of hemolysis**
- **DAT does not diagnose all causes of hemolysis (non-immune causes) in newborns and only identifies some infants as being at risk for hemolysis**
- **Many steps are required with an increased chances of error - from collection of blood to reporting of positive result**
- **Time consuming process**
- **Invasive blood draws for infants and adults**
- **Expensive laboratory costs**

ETCO and Neonatal Hyperbilirubinemia

Bilirubin, Jaundice, and Newborns

- **Neonates are born with an overabundance of red blood cells which the body quickly catabolizes as the baby's metabolism becomes established**
- **The catabolic process typically peaks within the first 72 hours after delivery, then diminishes as RBC counts decreases**
- **Elevated bilirubin levels result in jaundice, a disorder detected visually due to skin coloration**
- **Monitoring of bilirubin production is critical in preventing kernicterus, a devastating condition that can result in:**
  - **Potential brain damage from severe to subtle**
  - **Hearing loss and other neurological defects**

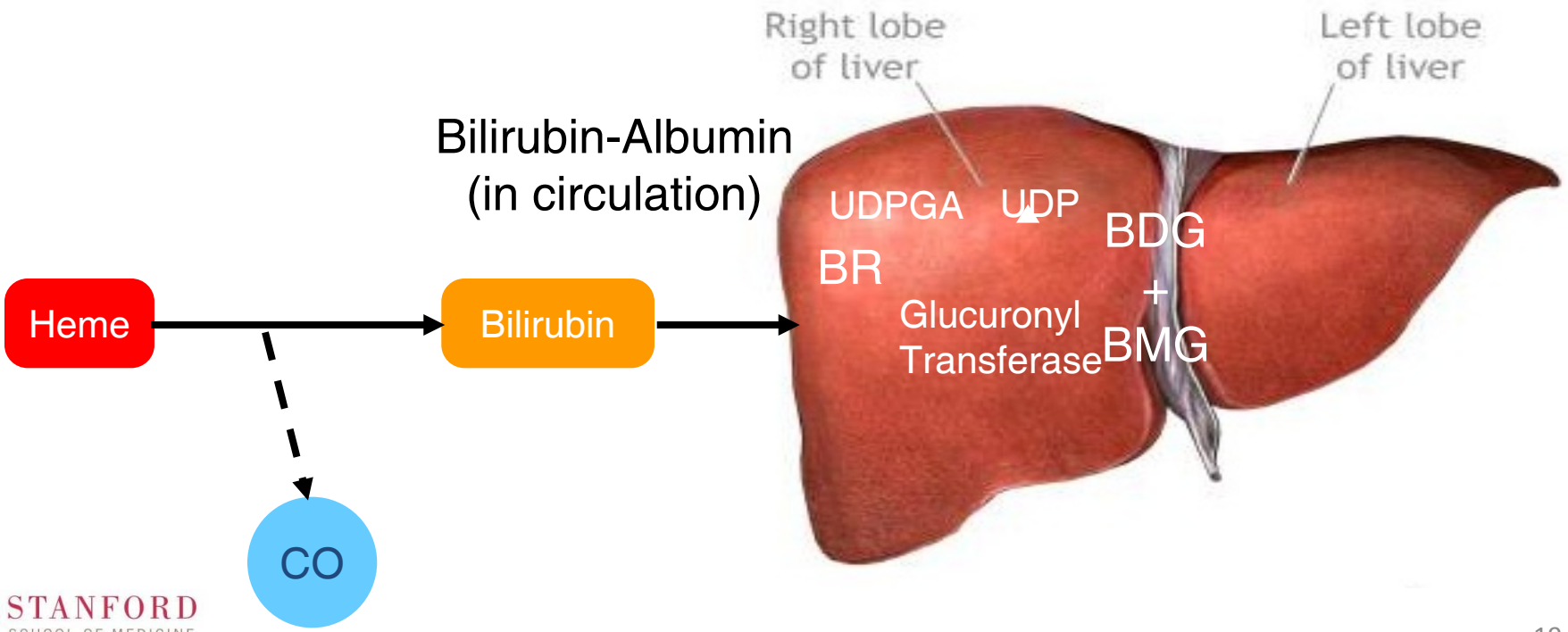
Neonatal Hyperbilirubenemia

- **Can be exacerbated by:**
  - **Blood group incompatibility with mother**
  - **Red cell enzyme deficiencies**
  - **Red cell membrane abnormalities**
  - **Breakdown of extravascular blood**
  - **Infection**
  - **Maternal diabetes**
  - **Polycythemia**
  - **Unknown ethnicity factors**

- **Identification of hemolysis is necessary to establish a care plan**

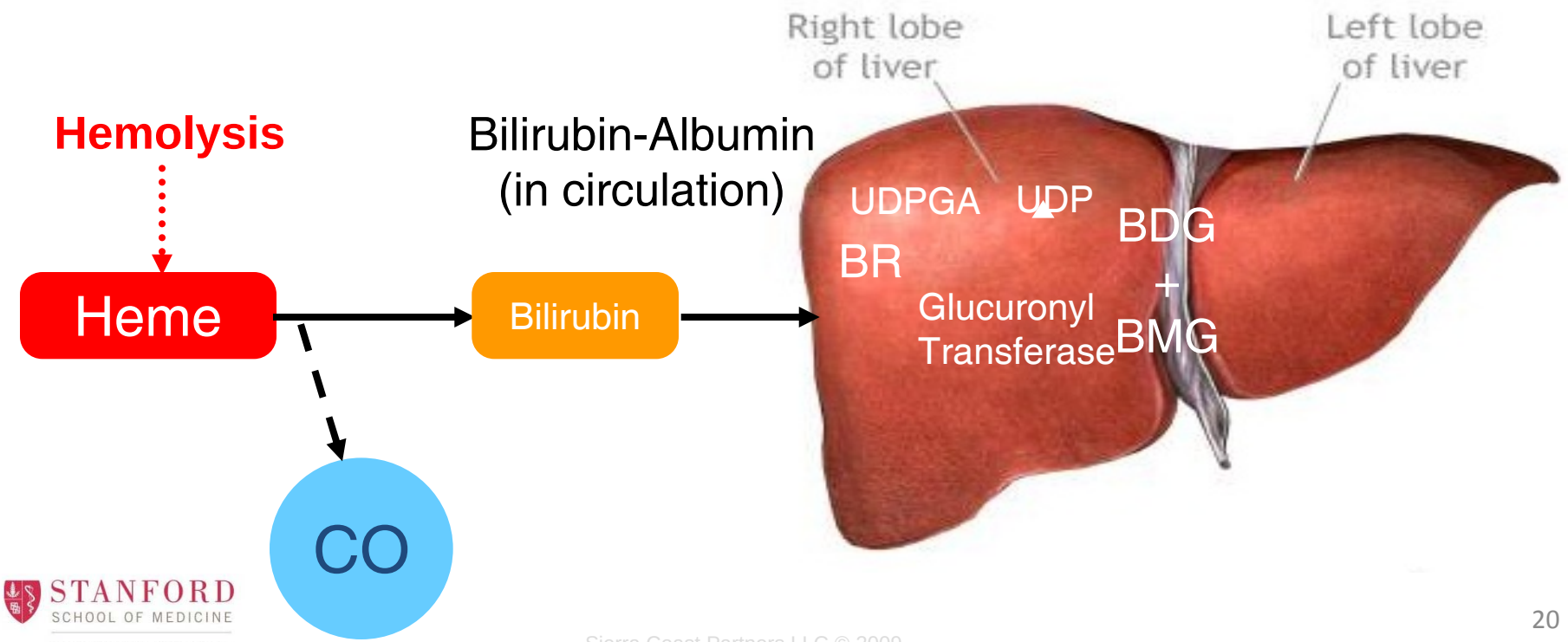
Bilirubin Production, Transport, and Elimination

- **Bilirubin is excreted by the liver after conjugation**
- **Newborn liver glucuronyl transferase (GT) is not induced until after birth and takes days to reach a level to keep up with bilirubin production**



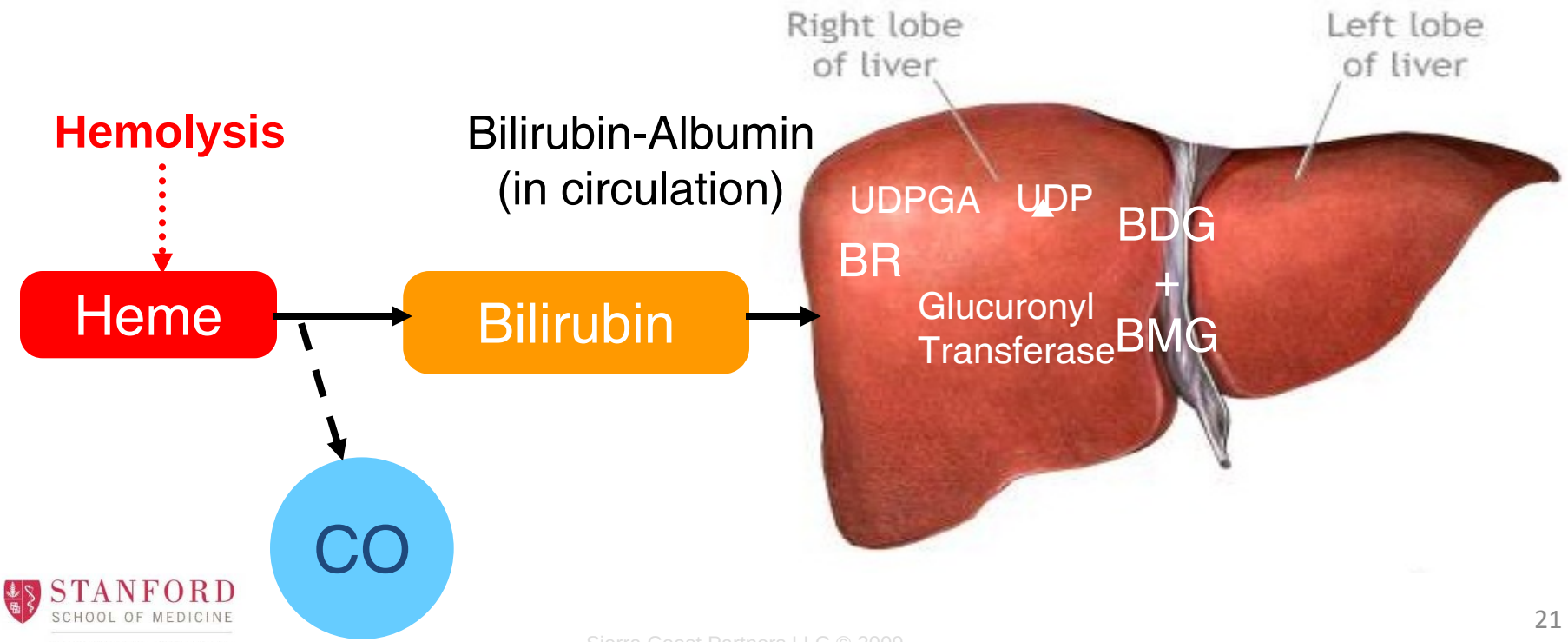
Bilirubin Production, Transport, and Elimination

- **Hemolysis exacerbates this normal lack of GT activity**

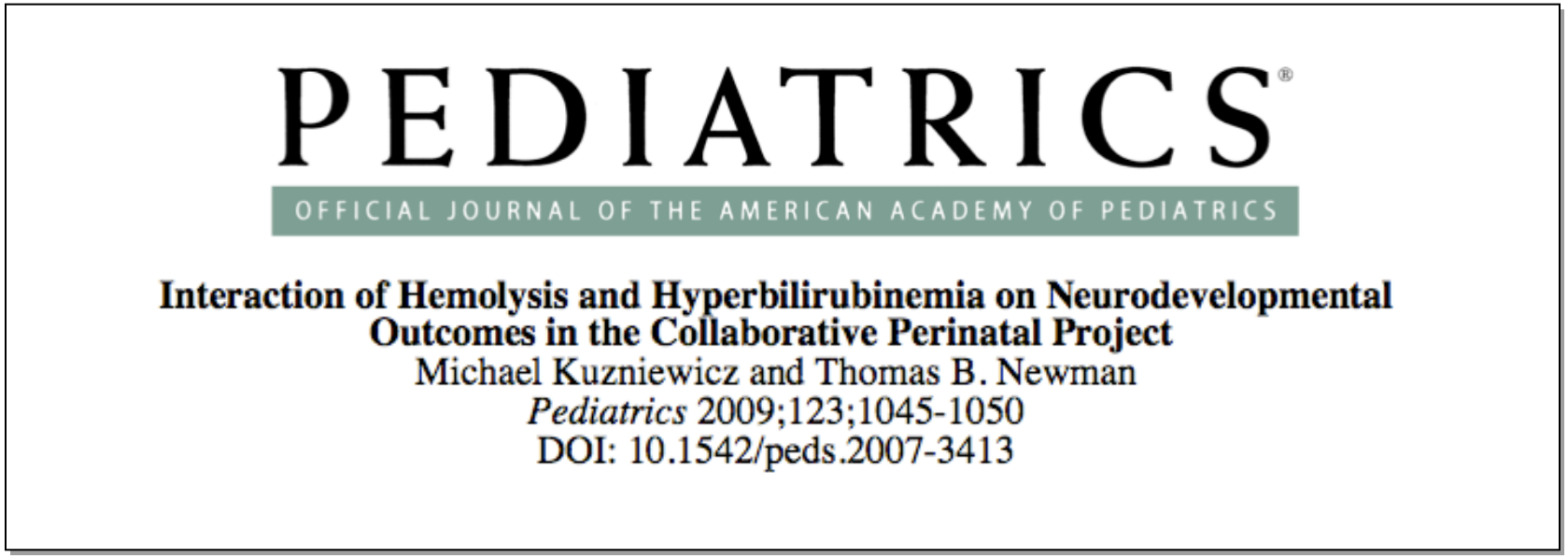


Bilirubin Production, Transport, and Elimination

- **Hemolysis exacerbates this normal lack of GT activity**



Infants with Hemolysis and Hyperbilirubinemia Are at Elevated Risk for Neurologic Damage



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Interaction of Hemolysis and Hyperbilirubinemia on Neurodevelopmental Outcomes in the Collaborative Perinatal Project

Michael Kuzniewicz and Thomas B. Newman

Pediatrics 2009;123;1045-1050

DOI: 10.1542/peds.2007-3413

- **Landmark analysis tracked 54,795 newborns from birth to 7+ years of age**
- **Published April 2009**
- **Investigated whether bilirubin is more neurotoxic in newborns with a positive direct antiglobulin test (DAT)**

Pediatrics Journal Study Conclusions

- **Significant association between a positive DAT and lower full-scale, verbal, and performance IQ scores for infants with TSB levels ≥25mg**

TABLE 3 Adjusted Wechsler-Intelligence Scale IQ Scores According to TSB Level and DAT Result, Including Interaction Term Between TSB Level and DAT Result

	Maximum TSB, Mean (95% CI)		
	<20 mg/dL	20 to 24.9 mg/dL	≥25 mg/dL
Full-scale IQ[a]			
DAT-negative	96.8 (95.3 to 98.2)	97.7 (96.0 to 99.4)	97.8 (93.5 to 102.0)
DAT-positive	98.9 (97.4 to 98.7)	98.1 (94.5 to 101.7)	93.2 (89.4 to 97.1)
Difference	2.1 (1.4 to 2.8)[b]	0.4 (−4.1 to 4.8)	−4.5 (−10.4 to 1.4)
Verbal IQ[a]			
DAT-negative	95.1 (93.5 to 96.6)	96.3 (94.5 to 98.1)	96.3 (90.5 to 102.0)
DAT-positive	96.5 (94.4 to 98.6)	96.1 (92.3 to 99.8)	91.3 (85.7 to 97.0)
Difference	1.5 (0.7 to 2.3)	−0.3 (−4.3 to 3.8)	−5.0 (−14.4 to 4.5)
Performance IQ[a]			
DAT-negative	99.3 (98.1 to 100.4)	99.6 (97.3 to 102.0)	99.7 (96.3 to 103.1)
DAT-positive	101.7 (100.3 to 103.1)	100.6 (96.0 to 105.2)	96.3 (91.8 to 100.7)
Difference	2.4 (1.9 to 2.9)	1.0 (−5.1 to 7.1)	−3.5 (−8.0 to 1.1)

[a] Adjusted for race, gender, gestational age, maternal education, SGA, feeding method, birth weight, and (birth weight)^2.

[b] Difference may not equal the differences between DAT-negative and DAT-positive IQ scores because of rounding.

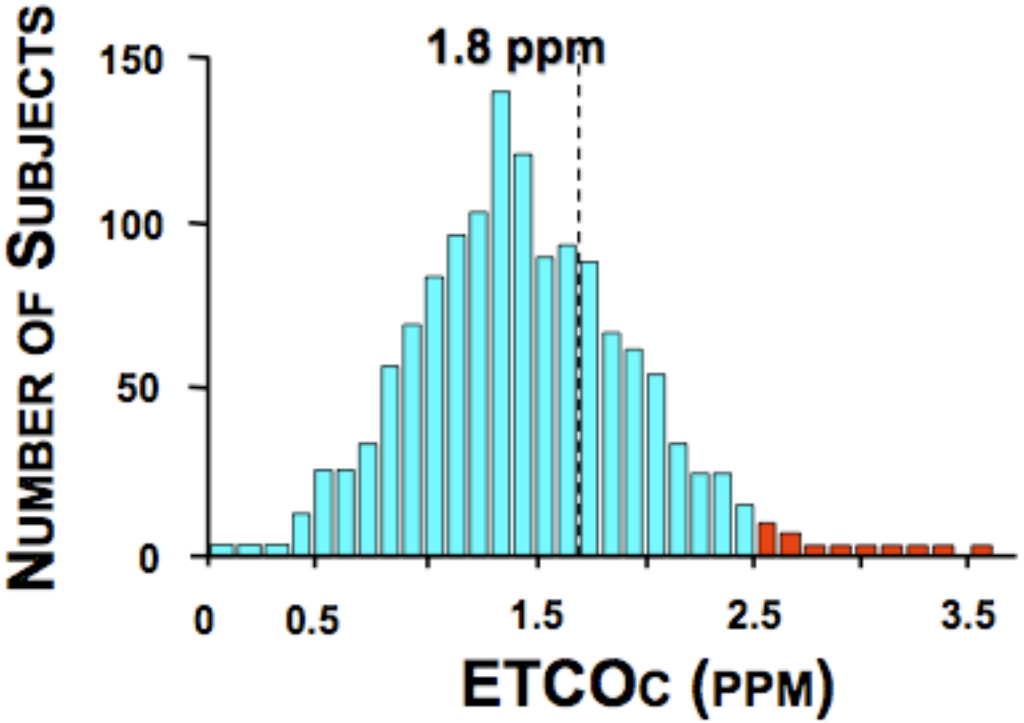
Clinical Diagnosis of Hyperbilirubinemia

- **Currently there are no tests in common that can reliably diagnose newborn hemolysis**

- **Existing methods to identify neonates at birth who are at higher risk for hemolytic disease:**
  - **Screening by Blood Bank on umbilical cord blood for ABO group**
  - **Rh type**
  - **Frequent TSB (Total Serum Bilirubin) levels**
    - **TSB levels do not differentiate jaundice casued by high bilirubin production**
  - **Coombs DAT: inaccurate at identifying all infants at risk**
    - **Heel stick, blood sample**
    - **Repeated tests are required to monitor**

ETCO: An Indicator of Elevated Hemolysis

- **Neonates who developed hyperbilirubinemia (TSB>95th percentile) had distinctly higher ETCO values than control population**



From Stevenson et al. Pediatrics 108:31-9, 2001

STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

Coombs Test vs. ETCO

Journal of Perinatology

Evaluation of the Direct Antiglobulin (Coombs') Test for Identifying Newborns at Risk for Hemolysis as Determined by End-Tidal Carbon Monoxide Concentration (ETCOc); and Comparison of the Coombs' Test With ETCOc for Detecting Significant Jaundice

Marguerite Herschel, MD
Theodore Karrison, PhD
Ming Wen, MS
Leslie Caldarelli, MD
Beverly Baron, MD

Journal of Perinatology 2002; 22:341 – 347

ETCO: Hemolysis sensitivity vs. DAT

- **N=660**
- **Positive predictive value (PPV) of DAT for significant hemolysis at 12 hours was 58.8%**

Journal of Perinatology

Journal of Perinatology 2002; 22:341–347

Table 3

(a) For detection of neonates with hemolysis* sensitivity, specificity, positive predictive value of the direct antiglobulin (Coombs') test†

DAT	12-hr ETCOc‡		Total
	≥3.2	<3.2	
Positive	10	7	17
Negative	16	466	482
Total	26	473	499

Sensitivity of DAT: 10 of 26 = 38.5% (95% CI: 20.2–59.4).
Specificity of DAT: 466 of 473 = 98.5% (95% CI: 97.0–99.4).
Positivr predictive value of DAT: 10 of 17 = 58.8% (95% CI: 32.9–81.6).

(b) For detection of neonates with hemolysis§ sensitivity, specificity, positive predictive value of the direct antiglobulin (Coombs') test†

DAT	24-hr ETCOc‡		Total
	≥2.5	<2.5	
Positive	4	12	16
Negative	43	504	547
Total	47‖	516	563

Sensitivity of DAT: 4 of 47 = 8.5% (95% CI: 2.4–20.4).
Specificity of DAT: 504 of 516 = 97.6% (95% CI: 96.0–98.8).
Positive predictive value of DAT: 4 of 16 = 25.0% (95% CI: 7.3–52.4).

CI, confidence interval.
*Nonsmoking population. Hemolysis defined as ETCOc ≥95th percentile (≥3.2).
†DAT (one DAT result missing).
‡ETCOc, μl/l.
§Neonates of all mothers. Hemolysis defined as ETCOc ≥95th percentile (≥2.5).

STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

Journal of Perinatology Study - Conclusions

- **DAT fails to identify over half of the cases of significant hemolysis that are diagnosed by end-tidal carbon monoxide**

- **ETCO offers better predictive value than DAT which potentially identifies need for prompt intervention for at risk newborns**
  - **DAT does not diagnose hemolysis in newborns and it identifies as being at risk only some infants who have hemolysis**
  - **A neonate with a positive DAT has about a 59% chance of having significant hemolysis**
  - **Failure to recognize hemolysis is known to be a risk factor for severe hyperbilirubinemia and kernicterus**

- **End-tidal carbon monoxide may also provide a more sensitive index for predicting significant jaundice**

American Academy of Pediatrics Clinical Practice Guidelines (July 2004)

AAP POLICY

PEDIATRICS Vol. 114 No. 1 July 2004, pp. 297-316

CLINICAL PRACTICE GUIDELINE

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

Subcommittee on Hyperbilirubinemia

FUTURE RESEARCH

Identification of Hemolysis

Because of their poor specificity and sensitivity, the standard laboratory tests for hemolysis (Table 1) are frequently unhelpful.[66,67] However, end-tidal carbon monoxide, corrected for ambient carbon monoxide ($ETCO_c$), levels can confirm the presence or absence of hemolysis, and measurement of $ETCO_c$ is the only clinical test that provides a direct measurement of the rate of heme catabolism and the rate of bilirubin production.[68,69] Thus, $ETCO_c$ may be helpful in determining the degree of surveillance needed and the timing of intervention. It is not yet known, however, how $ETCO_c$ measurements will affect management.

- **However, the ability to measure ETCO in the clinic has been limited only by the lack of an accurate, simple, rapid, non-invasive testing device…**

ETCO: Limited Existing Diagnostic Methods

- **Mass spectroscopy or gas chromotography**
  - **Uses syringe to analyze ETCO breath**
  - **Requires skilled, trained user to observe chest wall movements of infant**
  - **Complex analytical equipment**
  - **Time and transport**
  - **Poor accuracy, requires predictable breathing cycle**

- **Chemical electrochemical sensors**
  - **Sensitive to many other gases as well as CO, susceptible to error**
  - **Slow response time**
  - **Discrete (vs. continuous) samples of end tidal breath must be obtained**

CoSense™

End Tidal Carbon Monoxide Monitor

Product Overview

STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

Bedside CO Measurement: Clinical Diagnostic Benefits

- **Can be used to assist clinicians in several important ways:**
  - **Identify high bilirubin producers, even before the onset of jaundice, allowing the physician to plan in-patient and post-discharge care**
  - **Detect a newborn at risk for the development of adverse sequelae of hyperbilirubinemia**
  - **Allow the clinician to establish a differential diagnosis of the underlying cause of hyperbilirubinemia**
  - **Conversely, the ability to rule out elevated bilirubin production may provide sufficient information to avoid unnecessary intervention and safely discharge an infant at an earlier hour**

Improved ETCO Device

- **Pneumatic system that provides enhanced reliability and better performance in clinical setting:**
  - Non-continuous, self contained sensors: isolates CO, CO2, and H2
  - Unique system captures a sample of the patient's end-tidal gas and isolates the sample for CO analysis
  - Use of real time capnometry provides high fidelity determination of the breathing pattern over a range of breath rates
  - Design eliminates interference from outside variables
  - Sensor is replaceable to eliminate the need for field calibration

Description and Features

- **Product:**
  - **Approximately 2 pounds**
  - **Battery: Lithium Ion rechargeable; 20 tests after a full charge; 2+ years battery life**
- **User Interface:**
  - **LCD Touch Screen for user input test result display**
- **Patient record data base**
- **Components:**
  - **Disposable Nasal cannulas**
  - **Power cord / Battery charger**
  - **User replaceable CO Sensor module (eliminates the need for field calibration)**

Simple and Easy to Use

1. Prepare CoSense

- Press the ON/OFF Button
- Select Patient Record: New or Existing

2. Prepare the Patient

- Attach the cannula to CoSense
- Position the cannula tip slightly inside the patient’s nare

3. Test

- Press the START TEST command
- When the test is complete, the Main Screen will reappear and results will be displayed

4. Record Results

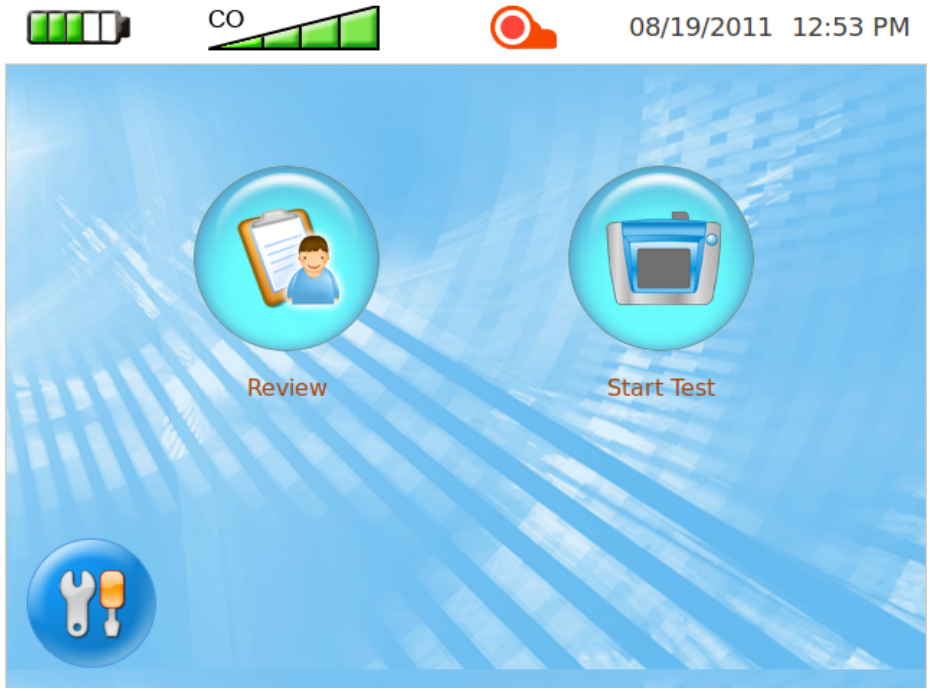
- Transcribe the results as desired. The result is also stored in CoSense and easily retrieved

5. Record Retrieval

- Enter patient name or ID to view all test records for that patient

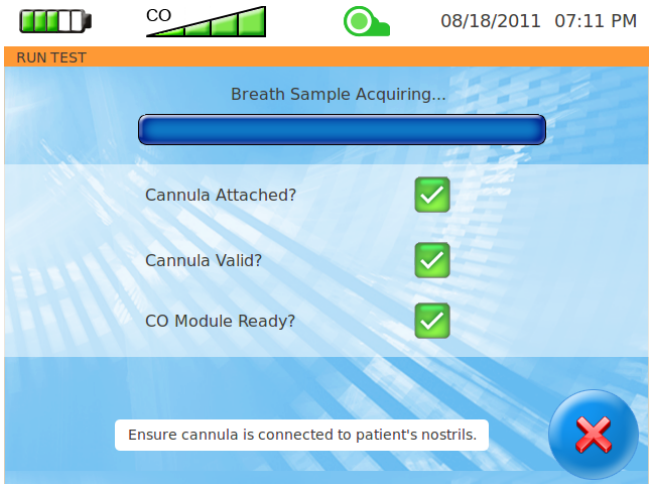
Basic Operation

- **Front Panel**
  - **Touchscreen Display**
  - **Battery level indicator**
  - **CO Sensor Expiration Date status indicator**
  - **Cannula Connection Status indicator**
  - **Date and time**
  - **Record Review or Start Test Options**
  - **Tools button (to access date and time settings and calibration info.)**

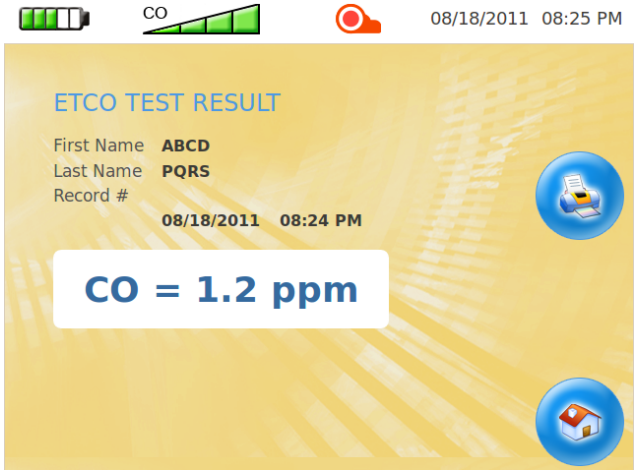


Basic Operation - Main Screens

Test Status Screen with status messages

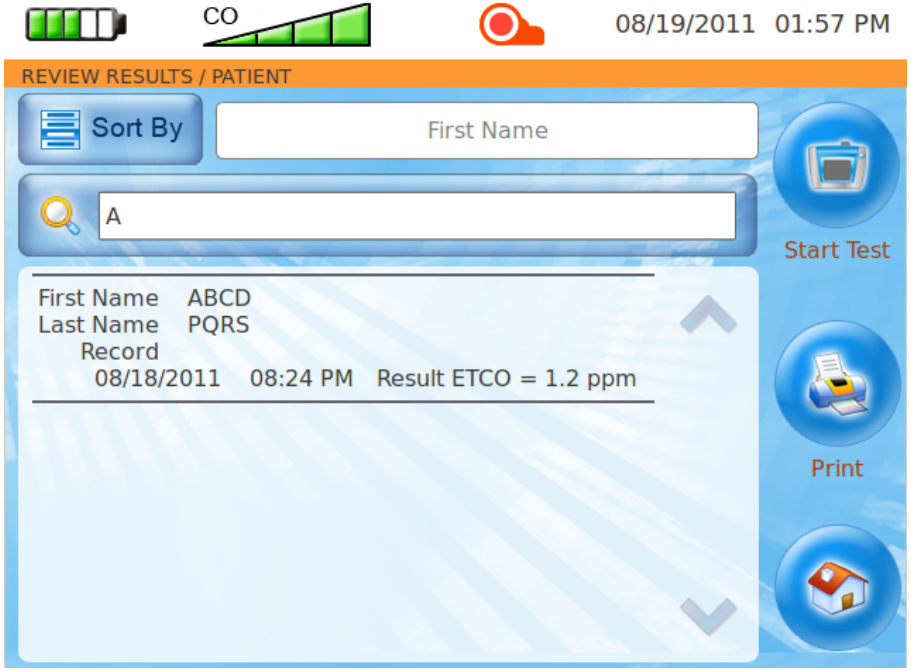


Test Result Screen



Patient Database

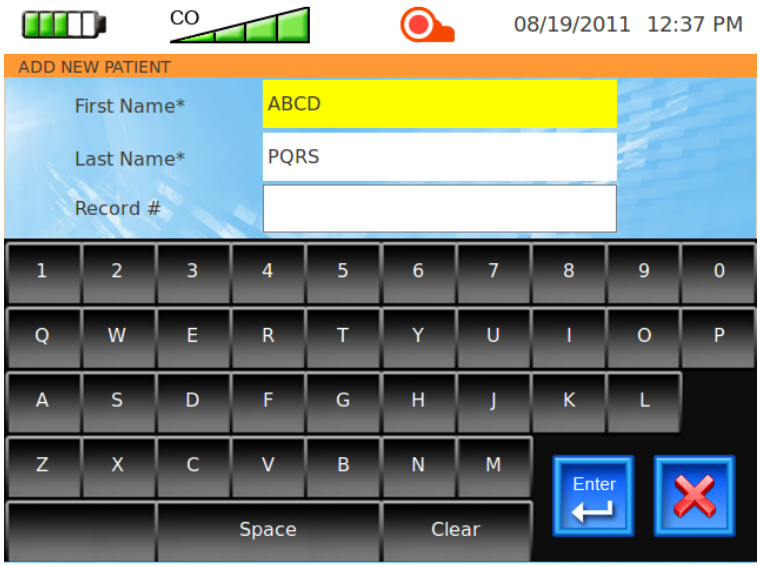
- **Record Storage**
  - **Stores up records for up to 300 patients and a total of 3000 records.**
  - **Stores:**
    - **Unique Patient ID**
    - **First and Last Name**
    - **Measurement Results**



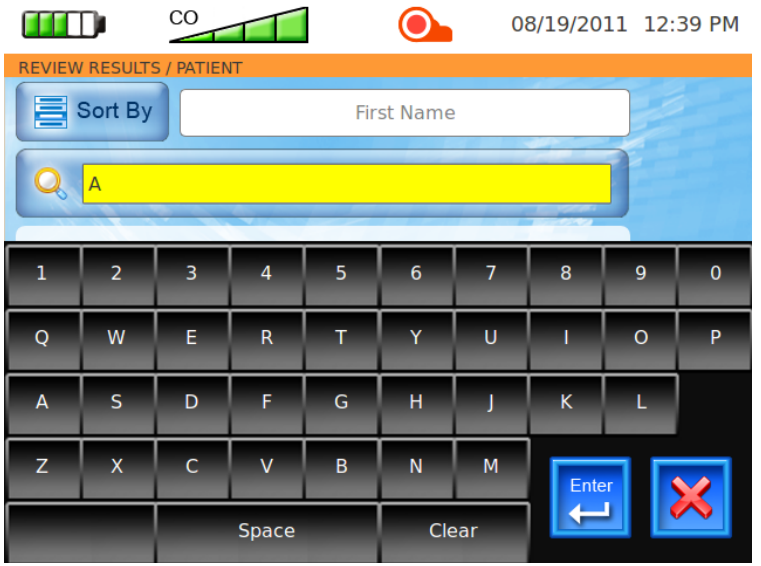
Patient Records

Virtual keyboard for….

Creating new patient records

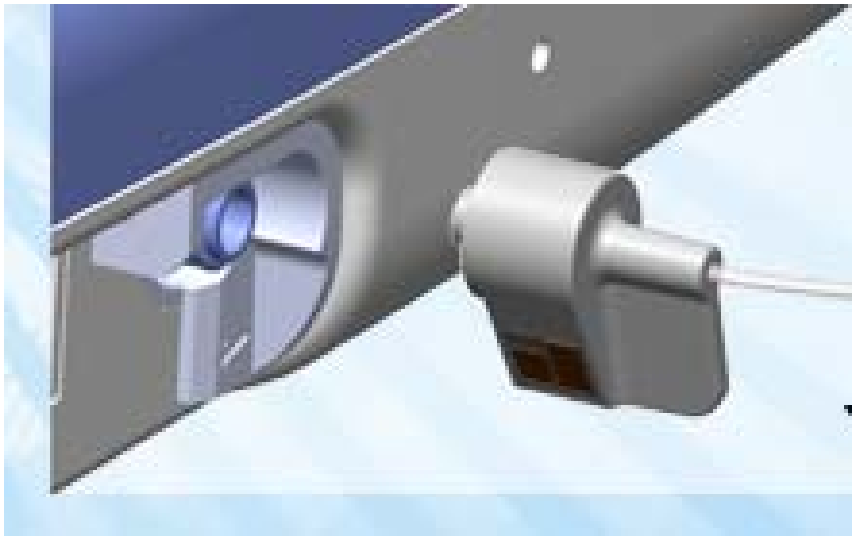


Accessing records of existing patient



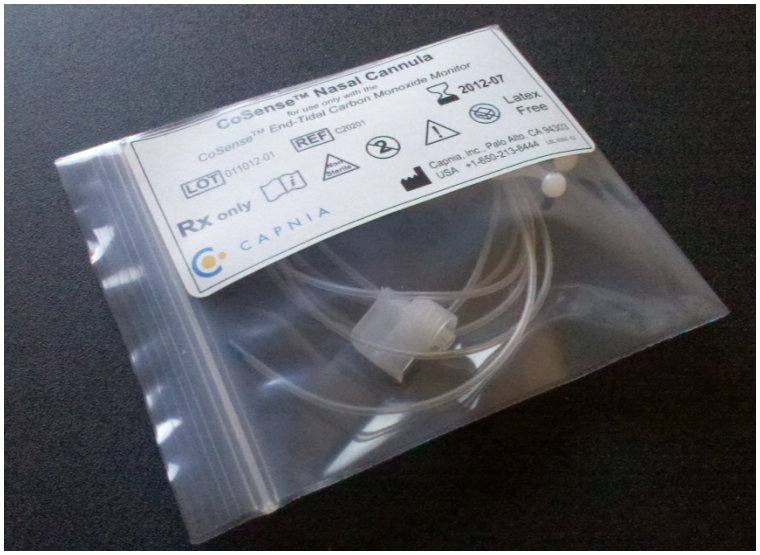
Cannula-Device Connection

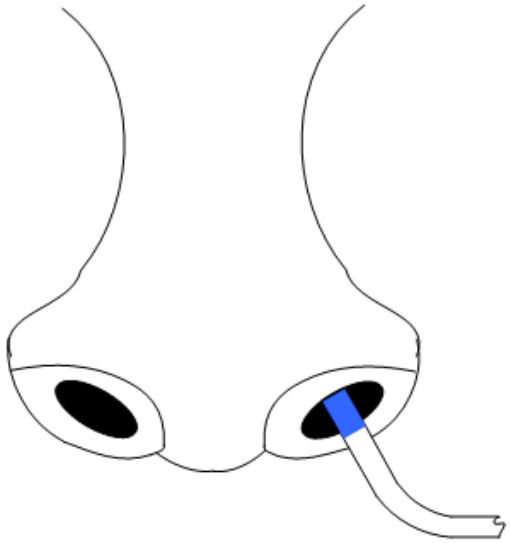
- **Connect the cannula via threaded lock connector**



Cannula Patient Connection

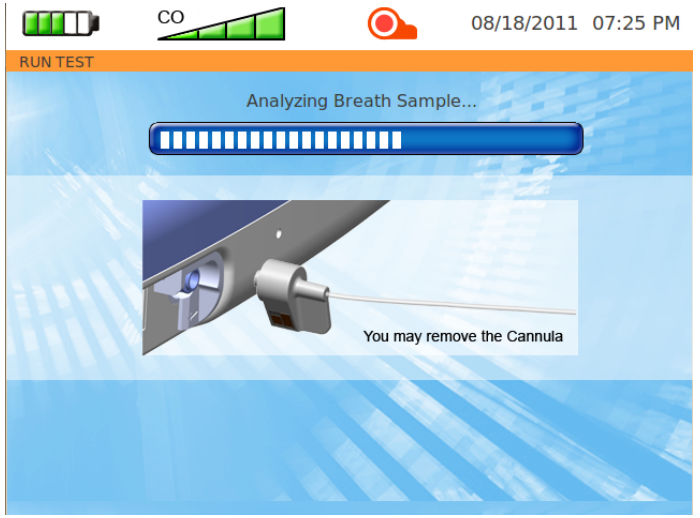
- **Place patient end of cannula just inside nares**
- **Attach to upper lip with adhesive strip**





Performing the Test: Results in Minutes

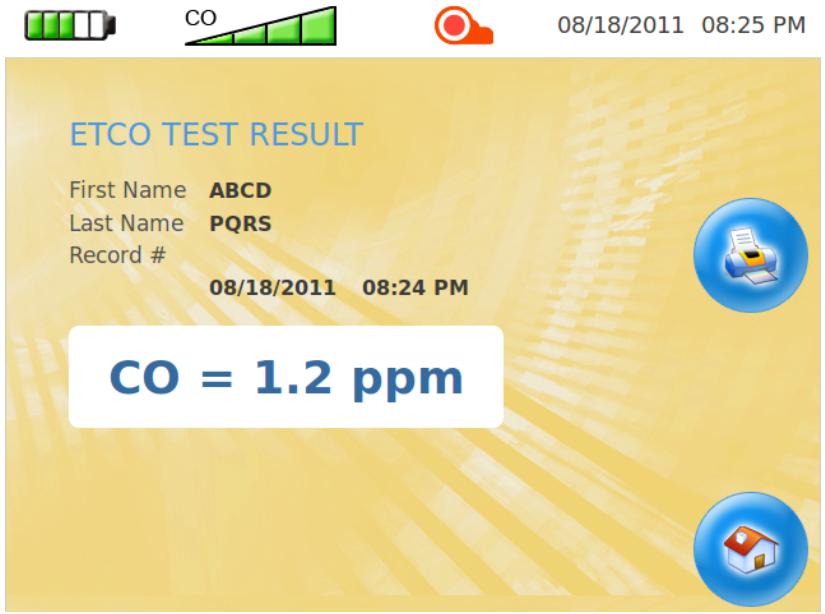
- **Test Sequence**
  - **“Preparing for Test”**
  - **“Breath sample acquiring”**
  - **“Analyzing Breath Sample”**
  - **“Flushing”**
  - **“Sampling Ambient Air”**
  - **“Analyzing Ambient Air Sample”**
  - **“Calculating ETCO result”**
  - **“Saving Data”**
  - **“Test Completed”**



Test Result

- **Patient ETCO (ppm) corrected for ambient**

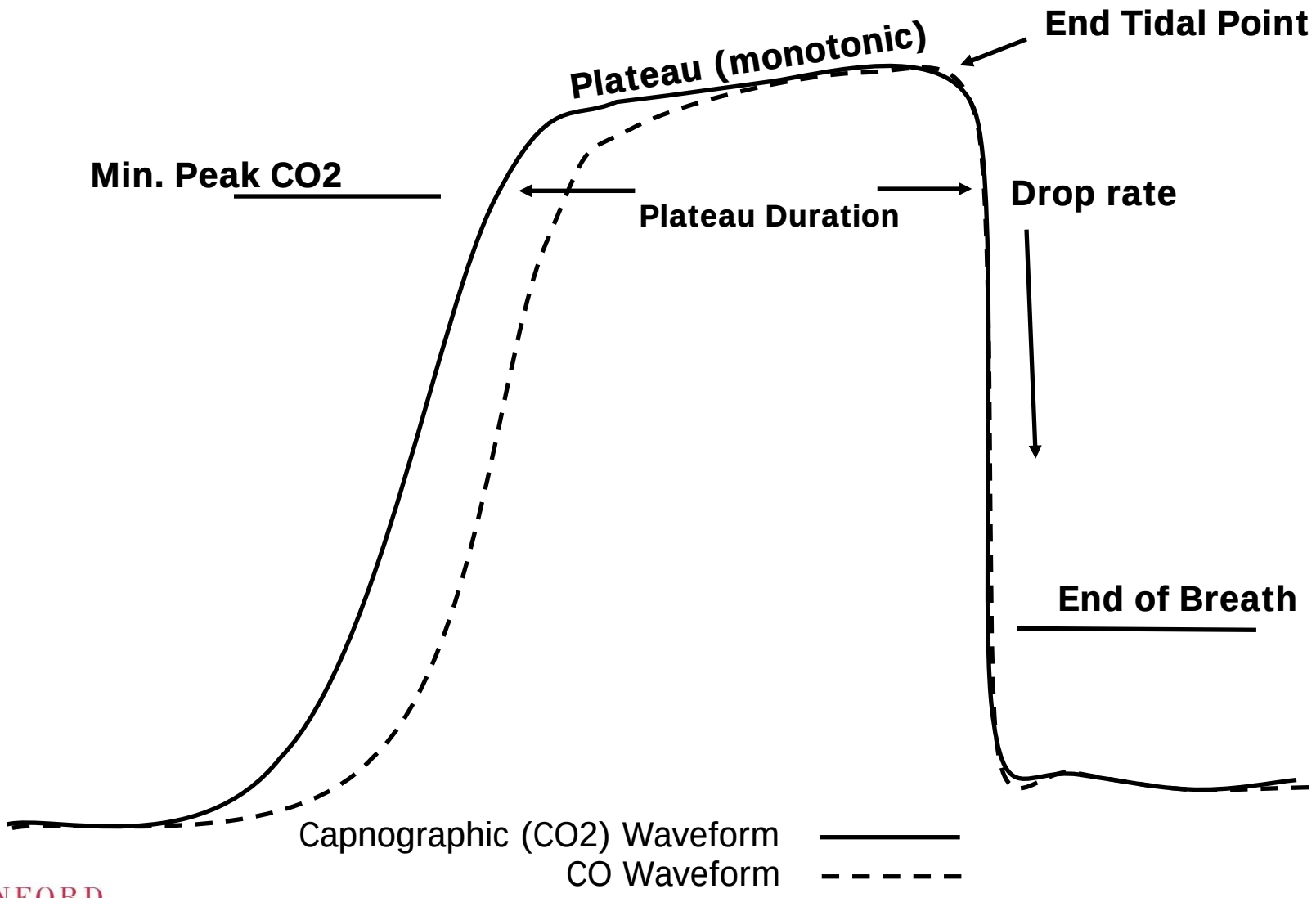
(Ambient CO, Breath H2 and Ambient H2, and breath rate are measured but not reported)



CoSense:How it Works

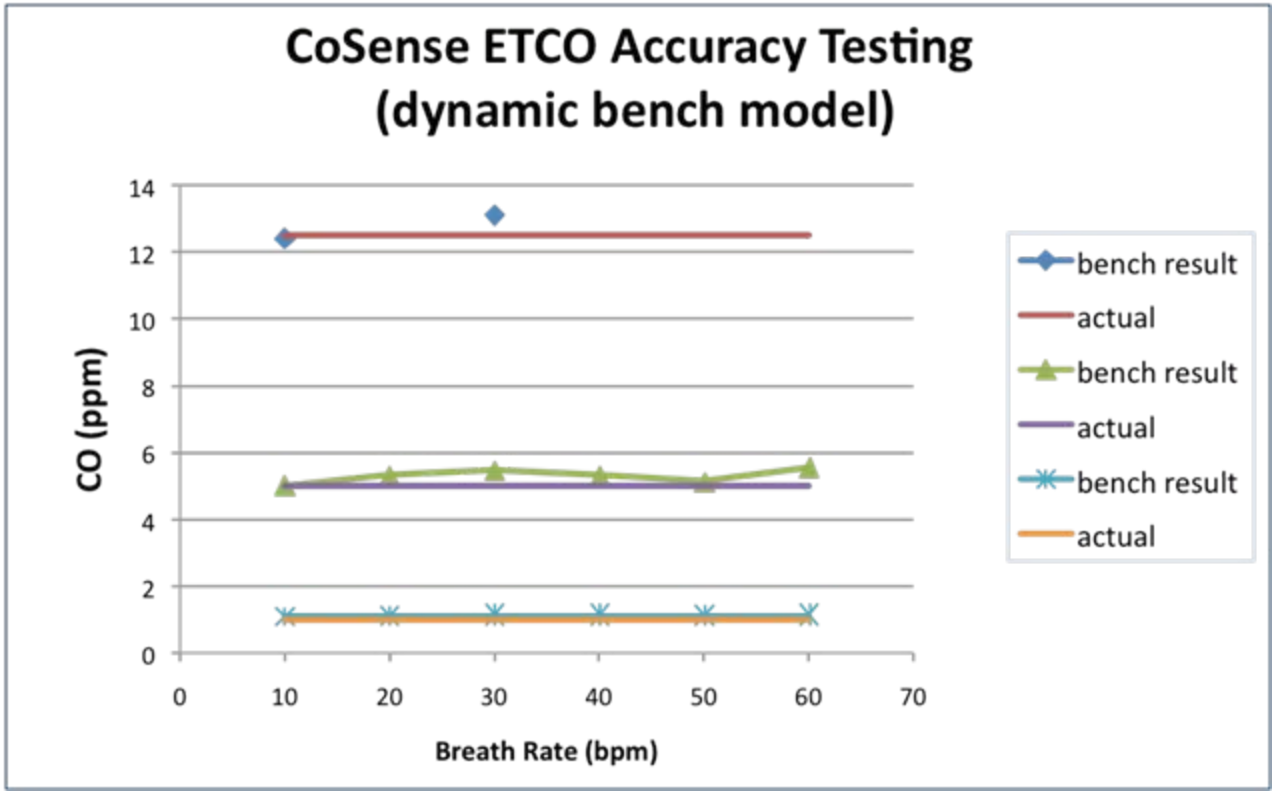
- **CoSense monitors the patient's breathing pattern**
- **After a valid breathing pattern is detected, an end-tidal gas sample is captured**
- **CO levels are then determined in this end-tidal gas sample**
- **CO concentration is determined based on signal response of the sensor, and the associated computational equations**
- **The physiologic ETCO level is determined by subtracting the ambient CO measurement from the Breath ETCO measurement**

Breath Analysis



STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

CoSense: Measuring ETCO



Physician and Hospital Benefits

- **Accurate identification of the rate of hemolysis:**
  - **Provides visibility to elevated hemolytic rate regardless of onset of hyperbilirubinemia**
  - **Meets AAP Practice Parameters**
  - **Superior to Coombs DAT test (false positives)**

- **Non-invasive**
  - **Non-disruptive to baby and Mom (baby can sleep or even suck on a pacifier, remains with Mom)**
  - **Infection control (no needle sticks or bodily fluid exposure)**

- **Rapid point of care screening:**
  - **Eliminates waiting time associated with lab tests**

- **Easy to use**
  - **Simple, requires minimal operator training**
  - **ALGO and ETCO testing can be performed simultaneously**

- **Cost effective**
  - **Reduces multiple invasive lab tests used in search for hemolysis**
  - **Labor efficient, saves personnel time and associated costs**

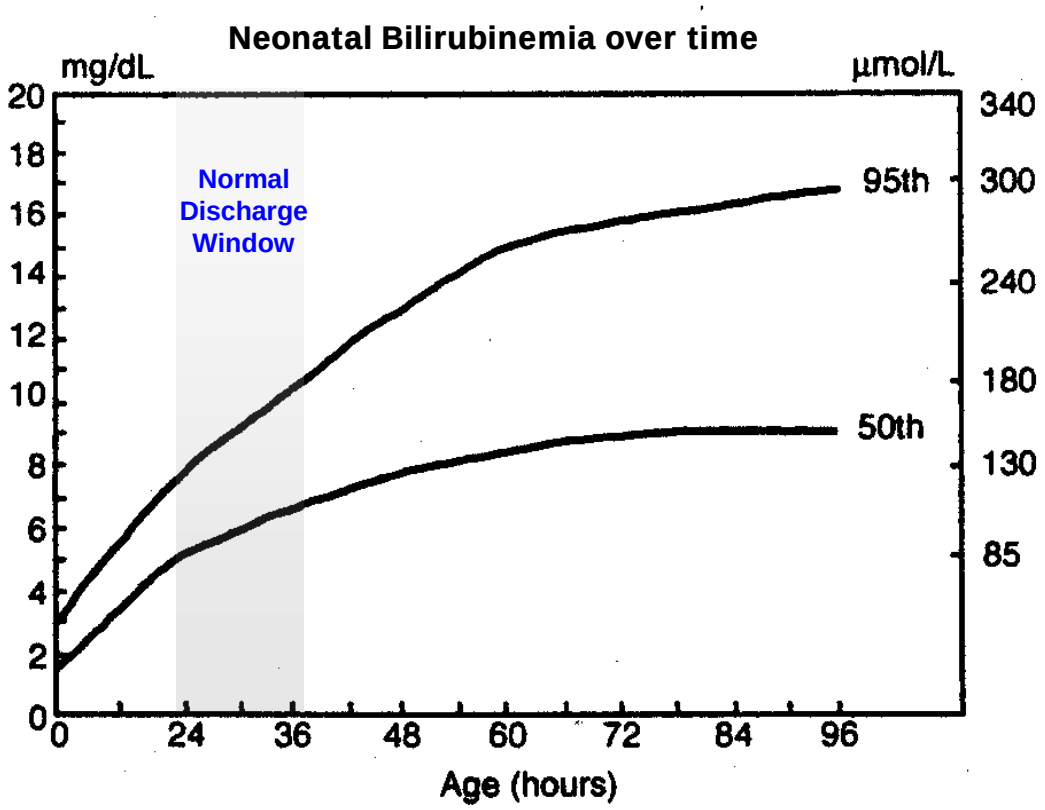
Improving Newborn Care

- **Est. worldwide annual births:**
  - **U.S. 4 Million**
  - **ROW 10.2 Million**
- **Healthcare cost of neonatal jaundice**
  - **60% of newborns become clinically jaundiced**
  - **Hospitals spend $1.3 Billion per year treating neonatal jaundice**
  - **Millions spent on DAT, other blood tests**

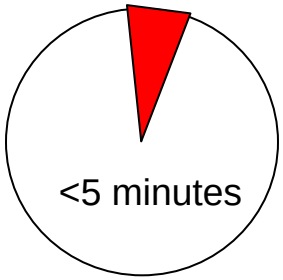
Sources: Centers for Disease Control (CDC), United Nations Statistics Division, American academy of Pediatrics Clinical Practice Guidelines October 1994
Dain Rauscher Wessels Analyst Reports

"Normal" Diagnosed Babies May Still Be At Risk

- **Cost containment strategies have created pressure to shorten stays: normal birth = 24 -36 hours**
- **<u>Bilirubin levels will continue to rise after the newborn has left the hospital, peaking > 72 hours</u>**
- **Places babies at risk for undiagnosed hyperbilirubinemia and readmission**



Utilizing the Device in the Newborn Nursery



STAT

Nomagram Result

"Low Risk"	**"Medium Risk"**	**"High Risk"**
Low TsB, Low ETCO	**Low TsB, High ETCO**	**High TsB, High ETCO**
Non-Hemolytic Newborns Physician can safely discharge baby early or on-time per hospital protocol.	**Hemolytic Newborns** Physician can discharge baby per hospital protocol Pediatrician Follow up within 24-36 hours	**Hemolytic Newborns** Perform additional tests to determine cause of hemolysis Patient stays in hospital

Summary

- **End-tidal CO is the most direct and accurate measurement of hemolysis**
- **A hand-held device can measure end tidal carbon monoxide – indicating hemolysis**
- **Offers significant advantages vs. current laboratory test procedures**
  - **More accurate and faster diagnosis**
  - **Less expensive**
  - **Non-invasive**
  - **Portable hand-held**
  - **Simple and easy to use for physicians and nurses**
- **Potential application diagnosing newborns at-risk for adverse outcomes of hyperbilirubinemia (jaundice)**

Risks of Hyperbilirubinemia and Phototherapy

GDAC Presentation

Thomas B. Newman, MD,MPH

Professor of Epidemiology and Biostatistics and Pediatrics, UCSF

3/13/12

Overview

- Background- basic paradigm
- Epidemiology of hyperbilirubinemia
  - Incidence
  - Risk factors
  - Treatment with phototherapy; NNT
- Epidemiology of kernicterus
  - Incidence
  - Cofactors
- Possible late risks of phototherapy

Basic Paradigm

- Goal is to prevent kernicterus, but kernicterus is hard to study – too rare.
- Hyperbilirubinemia causes kernicterus
- Therefore, study risk factors and treatments for hyperbilirubinemia instead

Incidence of hyperbilirubinemia -1

TSB ≥ 25 mg/dL (no screening)				
1st author, year	**Place, years**	**N cases**	**Total N**	**N/1000**
Kuzniewicz, 2009	USA, Northern CA, 1995-2006	422	319,904	1.32
Eggert, 2006	USA, Utah. 2001-2	32	48,798	0.66
Mah, 2010	USA, 116 hospitals, 2003-5	66	129,345	0.51

Incidence of hyperbilirubinemia -2

TSB ≥ 26.3 mg/dL (450 uMol/L; no screening)				
1st author, year	**Place, years**	**N cases**	**Total N**	**N/1000**
Bjerre, 2008	Denmark, 2002-5	113	249,308	0.45
Sgro, 2006	Canada, 2002-4	258	640,000	0.40

Incidence of hyperbilirubinemia -3

TSB ≥ 25 mg/dL with screening				
1st author, year	**Place, years**	**N cases**	**Total N**	**N/1000**
Eggert, 2006	USA, Utah 2003-4	13	52,483	0.3
Kuzniewicz, 2009	USA, Northern CA, 2005-7	14	38,182	0.4
Mah, 2010	USA, 116 hospitals, 2003-5	265	899,472	0.3

Incidence of hyperbilirubinemia -4

TSB ≥ 30 mg/dL (no screeening)				
1st author, year	**Place, years**	**N cases**	**Total N**	**N/100,000**
Eggert, 2006	USA, Utah. 2001-2	5	48,798	10
Manning, 2007	United Kingdom, 2003-5	108	1,500,052	7
Kuzniewicz, 2009	USA, Northern CA, 1995-2006	38	319,904	12
Mah, 2010	USA, 116 hospitals, 2005-8	11	129,345	9

Incidence of hyperbilirubinemia -5

TSB ≥ 30 with screening				
1st author, year	**Place, years**	**N cases**	**Total N**	**N / 100,000**
Eggert, 2006	USA, Utah 2003-4	3	52,483	5.7
Kuzniewicz, 2009	USA, Northern CA, 2005-7	2	38,182	5.2
Mah, 2010	USA, 116 hospitals, 2005-8	27	899,472	3.0

Risk factors for hyperbilirubinemia

- Increased production
- Decreased excretion
- Increased enterohepatic circulation

Score to predict TSB ≥ 25 mg/dL*

Variable	Points
Exclusive Breast Feeding	6
Previous infant with jaundice	6
Bruising	4
Asian Race	4
Cephalhematoma	3
Mother >= 25 yr	3
Male sex	1
~~Black Race~~	~~-2~~
Gestational age	2 * (40 - GA)

*Newman et al, Arch Ped Adol Med 2000; 154:1140-7

Risk Index for Predicting TSB ≥ 25 mg/dL*

Score	Percentiles	Likeli-hood Ratio	Posterior Probability
< 8	1-32%	0.053	1/15653
8-10	33-61%	0.36	1/2327
11-15	62-90%	1.5	1/540
16-20	91-98%	3.3	1/251
> 20	99%	18.2	1/47

333-fold variation in risk

*Newman et al, Arch Ped Adol Med 2000; 154:1140-7

Validation of Risk Index for TSB ≥ 25 mg/dL*

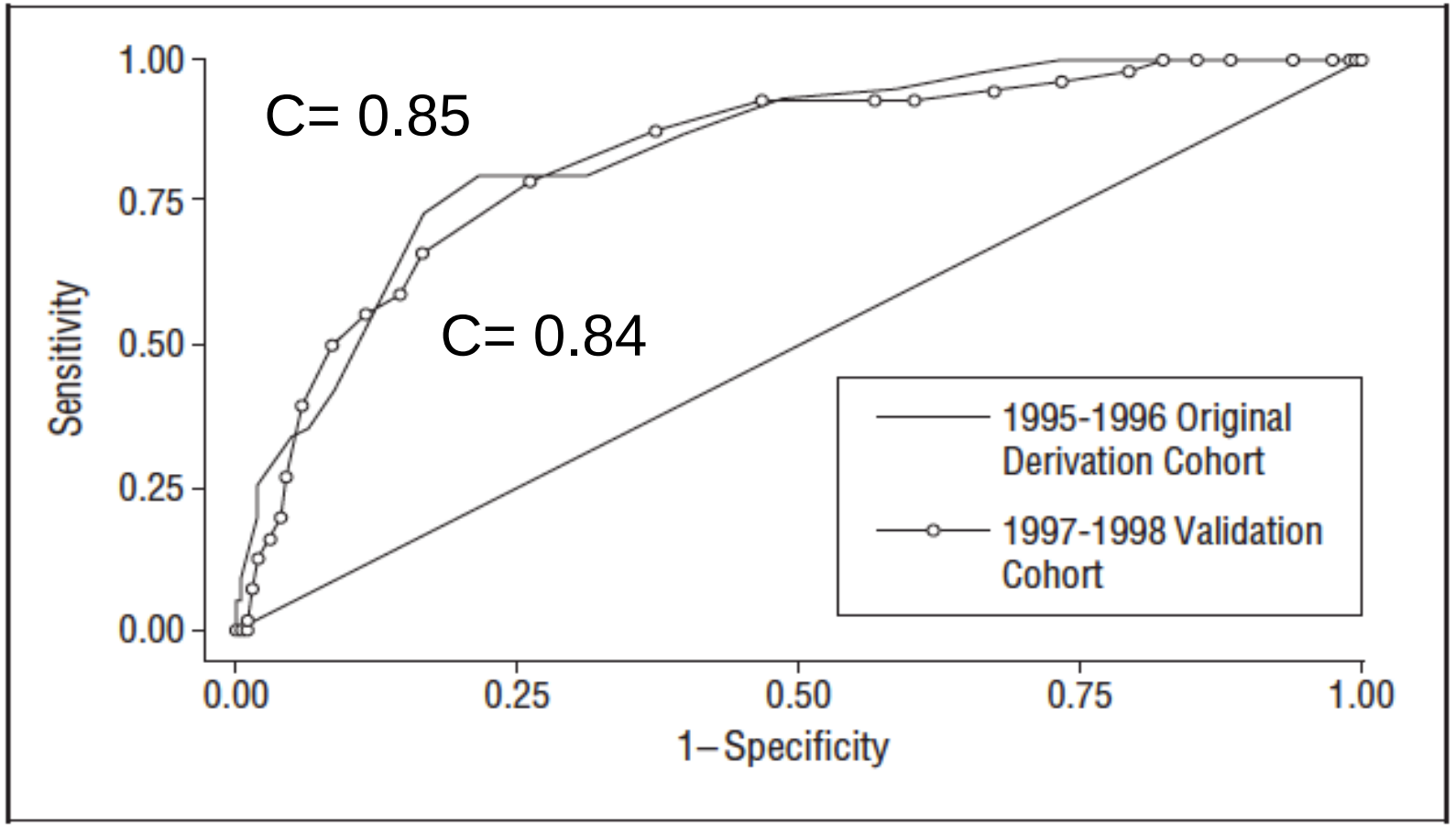


Figure 1. Receiver operating characteristic (ROC) curves for the modified risk index to predict total serum bilirubin level of 25 mg/dL (428 µmol/L) or higher, comparing the original derivation cohort (1995-1996) with the validation cohort (1997-1998).

*Newman TB et al. Arch Peds Adol Med, 2005

Multivariable model to predict TSB >= 25 mg/dL among untreated newborns with TSB 17-22.9 mg/dl at >= 48 hours, compared with controls matched on TSB and age*

Variable	Adjusted OR (95% CI)	P value
Gestational age		
40+ weeks	Reference	NA
38 to 39 weeks	3.12 (1.21 to 8.03)	.02
34 to 37 weeks	3.74 (0.62 to 22.7)	.15
Family history of jaundice	3.83 (0.93 to 15.7)	.06
Bruising noted on examination	2.36 (1.17 to 4.77)	.02
TSB increase ≥ 6 mg/dL/day	2.54 (1.17 to 5.50)	.02
Inpatient phototherapy*	0.15 (0.06 to 0.40)	< .001
Exclusive breast-feeding†	2.03 (1.03 to 3.99)	.04

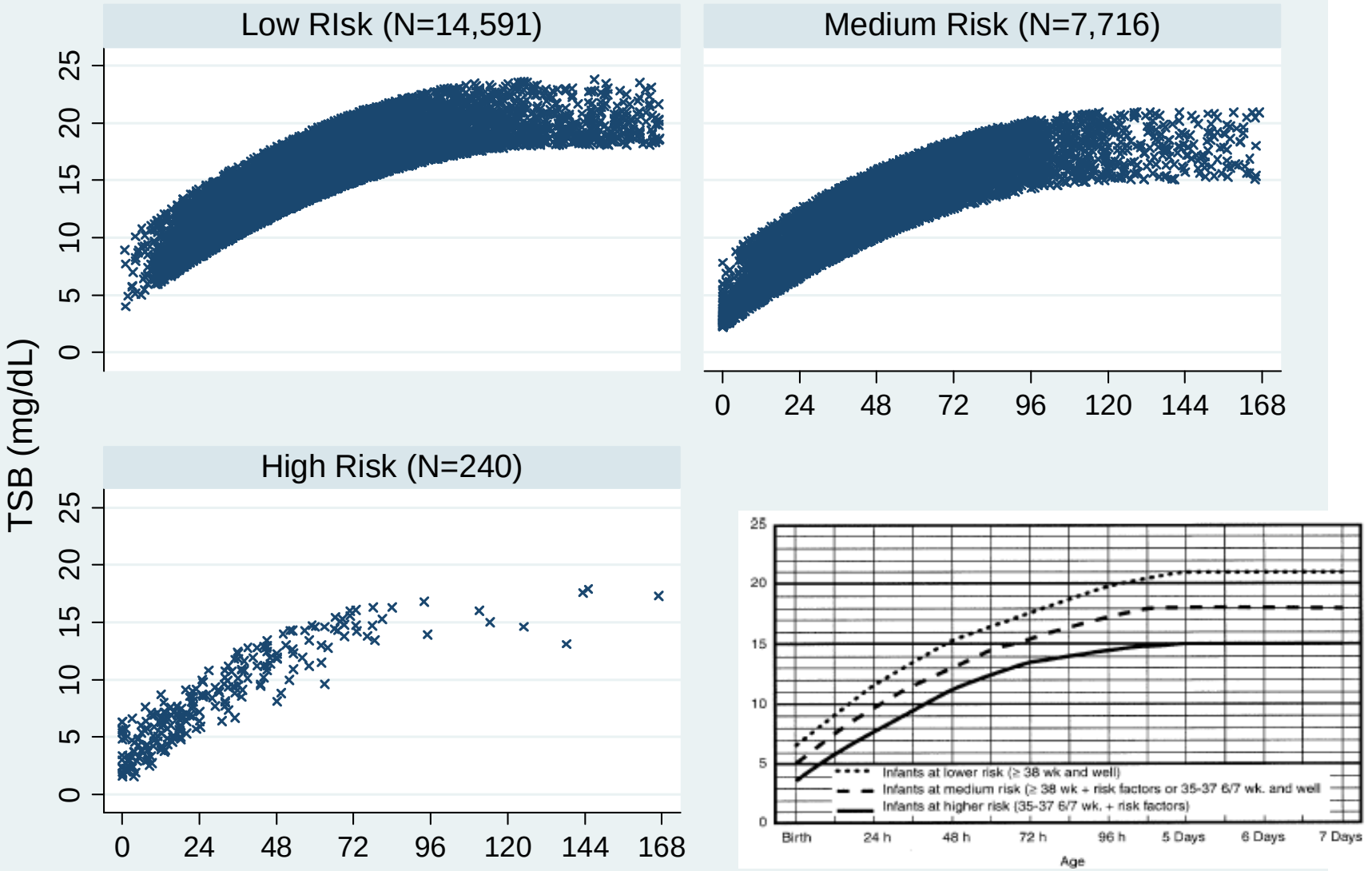
NA, not applicable.
*Inpatient phototherapy within 8 hours of qualifying TSB.
†Exclusive breast-feeding after reaching qualifying TSB.

*Kuzniewicz, M et al. *J Pediatr 2008;153:234-40*

Phototherapy: estimating efficacy and NNT

- Retrospective cohort study using electronically available data
- Setting: Northern California Kaiser Permanente Medical Care Program (12 hospitals, 1995-2004)
- Subjects eligible if ≥ 2000 g, ≥ 35 weeks and +/- 3 mg/dL from AAP phototherapy guideline (N=22,547)

“Qualifying” TSB levels



Outcome variable

- Crossing the AAP exchange transfusion threshold within 48 hours of qualifying TSB (linear interpolation)
- Rationale
  - Incorporates age and AAP risk group
  - If ET threshold crossed after 48 hours, initial decision not to do PT probably reasonable

Results

- 5251 (23%) received hospital phototherapy within 8 hours
- Only 187 (0.8%) crossed the ET line in < 48 h
- Only 3 received exchange transfusions

Newman TB, Kuzniewicz MW, Liljestrand P, Wi S, McCulloch CE, Escobar GJ . Numbers Needed to Treat with Phototherapy According to American Academy of Pediatrics Guidelines. Pediatrics 123(5):1352-9.

Results – Multivariate: Phototherapy

Variable	OR	P	95% CI	
Home PT within 1 day	0.29	0.312	0.03	3.19
Hospital PT within 8 h				
DAT- or missing	0.16	<0.001	0.07	0.33
DAT +	0.64	0.40	0.23	1.81
Interaction DAT+ and PT	4.10	0.002	1.7	10.1

Results: NNT (with inpatient PT) for 3.3 kg newborns with TSB 0-1 mg/dL above the AAP phototherapy threshold

Gestational Age, wk	NNTs (95% CI)			
	Age at Qualifying TSB: <24 h	Age at Qualifying TSB: 24 to <48 h	Age at Qualifying TSB: 48 to <72 h	Age at Qualifying TSB: ≥72 h
Boys				
35	14 (7–40)	26 (14–57)	83 (36–190)	171 (70–426)
36	10 (6–19)	19 (12–39)	59 (31–101)	122 (68–236)
37	16 (10–28)	29 (20–58)	95 (52–168)	196 (100–407)
38	35 (14–100)	67 (31–215)	222 (107–502)	460 (196–1352)
39	74 (31–244)	142 (62–554)	476 (197–1385)	989 (373–3607)
40	106 (44–256)	204 (98–487)	682 (367–1294)	1419 (634–3755)
≥41	148 (54–428)	284 (127–780)	953 (366–3017)	1983 (676–8408)
Girls				
35	21 (12–49)	40 (21–86)	126 (50–267)	261 (105–585)
36	15 (11–26)	28 (20–51)	90 (43–146)	186 (102–347)
37	23 (16–39)	44 (31–75)	145 (73–243)	300 (146–671)
38	53 (23–134)	102 (43–236)	339 (154–730)	705 (314–2016)
39	113 (58–342)	217 (103–713)	729 (272–1730)	1516 (614–4520)
40	162 (75–400)	312 (164–704)	1046 (491–2136)	2176 (922–6107)
≥41	226 (92–702)	435 (183–1140)	1461 (510–4842)	3041 (888–11096)

Newman et al. Pediatrics 2009;123:1352–1359

Problems with hyperbilirubinemia as a *surrogate outcome*

- Pathophysiology and causes of "hazardous" hyperbilirubinemia (TSB ≥ 30 mg/dL) may be different than those for less severe hyperbilirubinemia (e.g., TSB ≥ 20 mg/dL)

Relative risk of hyperbilirubinemia in black newborns compared with whites*

Definition of hyper-bilirubinemia (mg/dL)	RR	95% CI	P
≥ 20	0.64	(0.57 - 0.72)	< 0.001
≥ 25	1.17	(0.81 - 1.68)	0.4
≥ 30	4.22	(1.7 - 10.3)	< 0.001

*Wickremasinghe et al, in preparation. NC-KPMCP data 1995-2007 births, N= 216,807

Incidence of kernicterus

First Author, Year of Publi-cation	Country, years of birth	Case definition	Estimated population denom-inator	Estimated incidence /100,000
Manning, 2007	United Kingdom, 2003-5	Clinical course consistent with bilirubin encephalopathy, not normal at 12 months	1,500,052	0.7
Sgro, 2006	Canada, 2002-4	10 hearing loss; 2 motor problems; 2 seizures and 1 with vision problems; some overlap	640,000	2.0
Maimburg, 2009	Denmark, 1994-03	Validated KI dx: Acute enceph + TSB >= 26.3 + sequelae or death	710,533	1.1
Brooks, 2011	Calif-ornia, 1988-97	MD-assigned diagnosis in children receiving services for disabilities, adjusted for 10% mortality	~5.1 million	0.5

Importance of Comorbidity*

Table 6. Effect of risk factors and TSB on neurotoxicity (abnl neuro exam at death or discharge) among infants with TSB ≥ 25 mg/dL in Cairo

Group	N	Abnl	%
No risk factors, TSB < 30 mg/dL	64	0	0%
No risk factors, TSB ≥ 30 mg/dL	47	2	4%
ABO incompatibility, hct <35% (all)	38	1	3%
Sepsis/Rh, TSB < 30 mg/dL	16	10	63%
Sepsis/Rh, TSB ≥ 30 mg/dL	22	11	50%

*Gamaleledin et al. Pediatrics 2011;128:e1-e7

Conclusions

- Ballpark in developed countries without screening
  - TSB ≥ 25 mg/dL 1/1000
  - TSB ≥ 30 mg/dL 1/10,000
  - Screening reduces these levels of hyperbilirubinemia by 50-70%
  - Kernicterus (without screening) 1/100,000
- In Cairo, kernicterus generally requires Rh disease or sepsis in addition to hyperbilirubinemia

Provocative Thought

- Maybe kernicterus is rare in developed countries not so much because of better follow-up and use of phototherapy, but because of rarity of Rh disease and sepsis

Is phototherapy safe?

- Laboratory studies
  - Effects on DNA
- Epidemiologic studies
  - Weak evidence (single research group)
    - Diabetes
    - Asthma
  - Mixed evidence, some worrisome
    - Melanocytic nevi
    - Cancer, Leukemia, especially AML

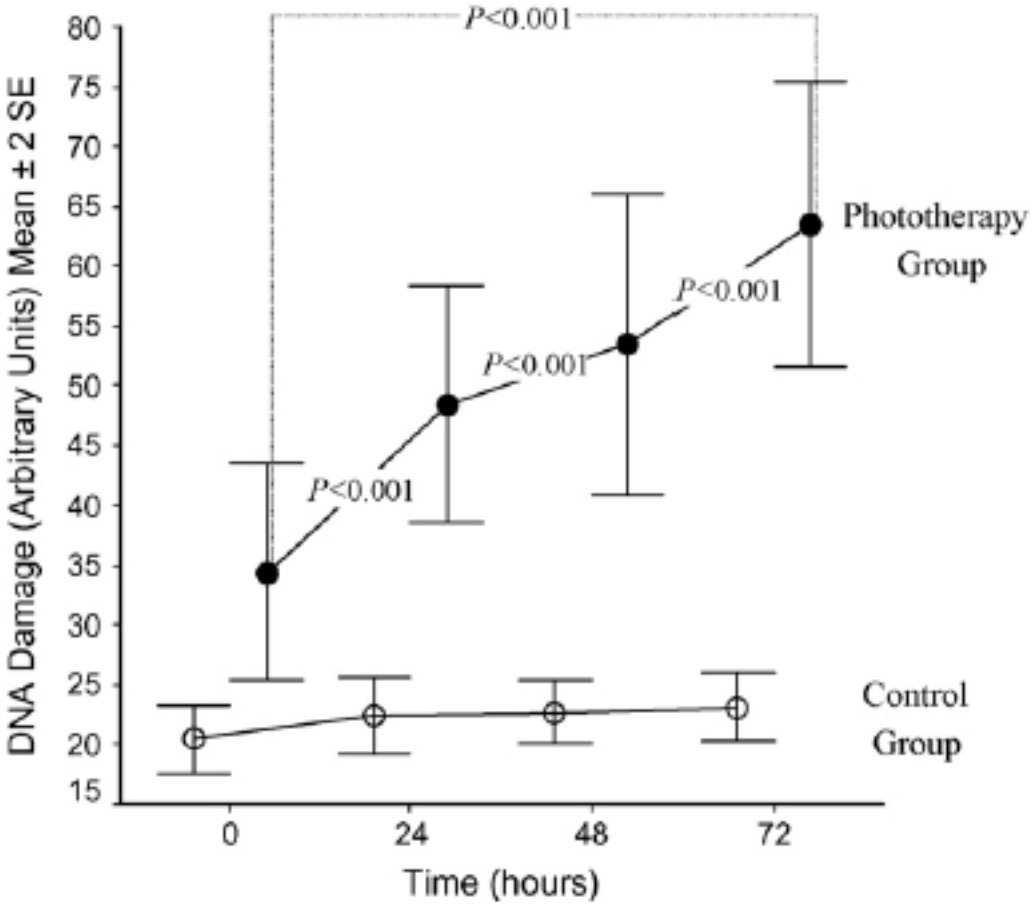
Mutagenicity of phototherapy

TABLE I. Mutagenicity of Visible Light for Salmonella typhimurium

Strain	Filter	Light absorbed by filter (nm)	kJ/m² at 450 nm	Mutants per plate
G46	None	–	0	3
G46	None	–	10	250
TA1530	None	–	0	35
TA1530	None	–	10	374
TA1535	None	–	0	27
TA1535	None	–	10	434
TA1538	None	–	0	26
TA1538	None	–	10	24
TA1530	None		10	430
	A	525-625	6.9	314
	B	345-420	6.7	404
	C	500-660	5.0	237
	D	500-650	4.7	181
	E	470-550	4.2	163
	F	470-620	2.3	136
	G	350-600	2.3	73
	H	350-590	0.2	18

Standard Ames test; i.e., revertants to histamine independence.
From Speck and Rosenkranz, Environ Mutagen 1979;1:321-36.

Comet test for DNA damage in newborns treated with phototherapy *



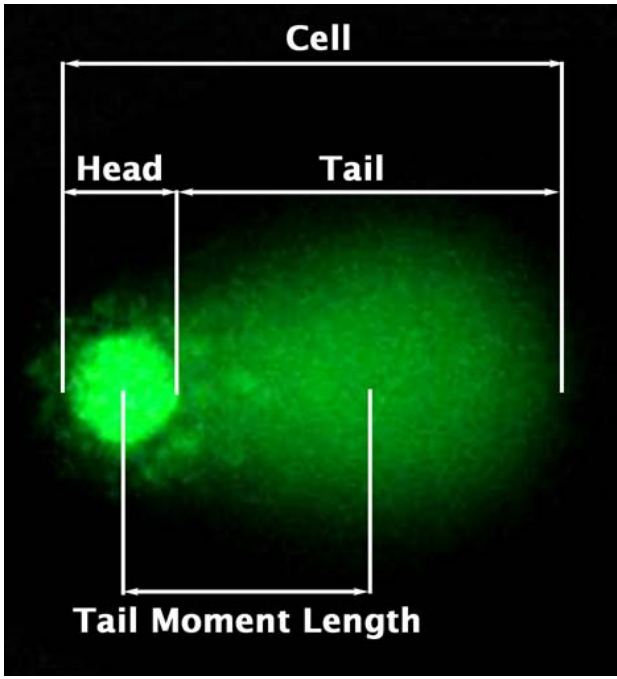


Fig. 1. Lymphocyte DNA damage in the two groups. Statistically significant differences were present between the two groups ($P<0.001$). The differences between sample points in the control group were not significant ($P>0.05$).

**M.M. Tatli et al. Mutation Research 654 (2008) 93–95*

Phototherapy and Leukemia

First Author, Year of Publication	Country	Years of birth	Type of Leukemia and N	Adjusted (if available) OR, (95% CI)
Cnattingius, 1995a	Sweden	1973-1989	Lymphatic (N=613)	1.0 (0.5, 1.8)
Cnattingius, 1995b	Sweden	1973-1989	Myeloid (N=93)	7.5 (1.8, 31.9)
Podwin, 2006	USA, WA state	1980-2002	All (N=595)	2.2 (1.0, 4.9)
Olsen, 1996	Denmark	1977-1989	Acute lymphocytoic (N=28)	1.1 (0.8, 1.7)
			All others (N= 6)	1.6 (0.6, 3.3)
Roman, 1997	England	~1954 to ~ 1985	Acute lymphoblastic (N=113)	0.6 (0.1, 3.4)
			Acute myeloid (N=15)	0 (0, 11.7)